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Adverse Drug Reactions with Antidepressants Drugs: Significance of Pharmacovigilance in Depression Pharmacotherapy

Antidepresan İlaçlarla Advers İlaç Reaksiyonları: Depresyon Farmakoterapisinde Farmakovijilansın Önemi

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ABSTRACT
Depression is a major public health psychiatric problem that affects people all over the world, with a high lifetime incidence and severe disability. Depending on the severity and pattern of depression episodes over time, antidepressant (ADs) medication may be advised as one of the therapeutic methods. On the other hand, ADs medication may have adverse drug reactions (ADRs). ADRs reduce people's quality of life, which leads to poor adherence to ADs, longer hospital stays, higher healthcare costs, poor therapeutic outcomes, physical morbidity, stigma and also death in the worst-case scenario. Psychiatrists must be familiar with the procedures for identifying and reporting ADRs, especially those that are new or unknown. Pharmacovigilance is a medical discipline based on these processes. Pharmacovigilance is not a "specialist" activity; it is a requirement for all those involved in the care of patients on medications, including doctors, nurses, and pharmacists and paramedical staff. This narrative review paper provides an overview of depression, ADs, Antidepressant-related ADRs, and the significance of pharmacovigilance. Articles were found using PubMed, Scopus, Google Scholar, MEDLINE and DergiPark databases. Firstly, we examined the title, then the abstract and finally the entire study. Depression appears to be associated with an increased risk of developing ADRs. Various ADRs are associated with ADs as per previously published literature. This review emphasizes the implementation of the pharmacovigilance system and the importance of monitoring ADRs in psychiatric depressive patients regularly by all healthcare professionals.
Keywords: Adverse drug reactions, antidepressants drugs, pharmacovigilance, depression, pharmacotherapy.

ÖZET
Depresyon, tüm dünyadaki insanları etkileyen, yaşam boyu insidansı yüksek ve ağır hastalık gösterebilen, önemli bir halk sağlığı psikiyatrik sorunudur. Zaman içerisinde depresyon ataklarının ciddiyetine ve ataklarına bağlı olarak, antidepresan ilaçları terapötik yöntemlerden biri olarak önerilmektedir. Öte yandan, antidepresan ilaçları advers ilaç reaksiyonlarına (AIR'ler) yol açabilir. AIR'ler insanların yaşam kalitesini düşürür, bu da antidepresanları kullanma isteksizliği, hastalıkta dalgalanmalara, hastanede kalma süresinin uzamasına, daha yüksek sağlık maliyetlerine, yeterli olmayan terapötik sonuçlara, fiziksel morbiditeye ve en kötü senaryoda ölüme neden olabilecektir. Psikiyatristler, özellikle de yeni veya bilinmeyen AIR'ları tanımlama ve bildirme prosedürlerine aşina olmalıdır. Farmakovijilans, bu süreçlere dayalı bir tıp disiplindir. Farmakovijilans bir 'uzmanlık' faaliyeti değildir; doktorlar, hemşireler, eczacılar ve paramedik sağlık personeli de dahil olmak üzere ilaç kullanan hastaların bakımıyla ilgilenen herkes için bir gerekliliktir. Bu anlatı derleme makalesi, depresyon, antidepresanlar, antidepresanla ilişkili AIR'ler ve farmakovijilansın önemi hakkında genel bir bakış sunmaktadır. PubMed, Scopus, Google Scholar, MEDLINE ve DergiPark veri tabanları kullanılarak makalelere ulaşılmıştır. Önce başlığı, sonra özeti ve son olarak da tüm çalışmayı inceledik. Depresyon, AIR gelişme riskinin artmasıyla ilişkili olduğu görünmektedir. Çeşitli AIR'ler, daha önce yayınlanmış literatüre göre antidepresanlarla ilişkilendirilmiştir. Bu derlemede, farmakovijilans sisteminin uygulanması ve psikiyatrik depresif hastalarda AIR'lerin tüm sağlık çalışanları tarafından düzenli olarak

izlenmesinin önemi vurgulanmaktadır.
Anahtar kelimeler: Advers ilaç reaksiyonları, antidepresan ilaçlar, farmakovijilans, depresyon, farmakoterapi

Introduction

Depression is a mental illness characterized by a persistent sense of sadness as well as a lack of enthusiasm for activities. Depression, also known as major depressive disorder (MDD) or clinical depression, affects a person's feelings, thoughts, behaviors and can result in a wide range of emotional and physical issues[1]. Depression may demand long-term treatment, and patients with depression benefit from one or both of these medications and psychotherapy treatments[2]. Such conditions cause more 'years lost' to incapacity than any other ailment. World Health Organization (WHO) reported that depression is the fourth leading cause of mortality among people aged 15 to 29, with more than 0.7 million cases of suicide per year worldwide[3].

Depression is widely misdiagnosed and mistreated due to stigma, a lack of appropriate treatments, and insufficient mental-health resources[4]. Depression is common as about 3.8% world population comprising 5% of adults and 5.7% of the geriatric population have been effected[5]. Every mood change and disturbing reactions are not the same as depression. Over 700,000 people commit suicide each year and such attempts are common among people who are depressed[6]. Mainly because therapeutic approaches exist for psychological problems, more than 75% of people in LMICs (low-middle-income countries) remain untreated. Inefficient treatment is attributed to a lack of funds, a shortage of trained healthcare professionals, and the societal stigma associated with mental illness[7].

Symptoms related to depression

Indications or signs may include a 2-week episode of depression marked by mood changes, loss of interest, or happiness. A lack of attention, feelings of excessive guilt or low self-worth, a sense of hopelessness about the future, thoughts of death or suicide are the reported symptoms of depression. Disrupted sleep, changes in appetite or weight loss/gain, and a state of weariness or poor concentration are some of the additional symptoms that could be present[8]. Specific individuals could more clearly express their mood shifts in the form of physiological symptoms in intercultural contexts, such as exhaustion, weakness, and discomfort. Physical symptoms, on the other hand, are unrelated to any other medical condition. Personal, family, social, educational, occupational, and/or other relevant areas of output are severely harmed during a depressive episode. The frequency and cruelty of symptoms, as well as the impact on the person's capability to function, define whether a depressive episode is mild, moderate, or severe[9].

There are numerous types of mood disorders; for example, depressive disorder is defined as a single episode of depression that happens at a specific time. The bipolar depression stated with the manic symptoms, such as euphoria or irritation, excitability, or energy, are common in such conditions. Other symptoms include decreased need for sleep, increased talkativeness, better self-esteem, competing thoughts, impulsive, and distractibility (quickly lose focus)[10].

Related factors and prevention

A person's depression is the result of a combination of factors and a complicated combination of social, psychological, and biological variables. People who have had setbacks in life (such as loss of employment or tragic events) are more likely to suffer from depression. Depression can worsen an individual's living circumstances, and the condition has a symbiotic link with physical health[11]. Previous study recommended various secondary preventive intervention for depression such as future research priorities include better defining intervention procedures, assessing treatment implementation, conducting more follow-up studies, and determining how different participants respond to early intervention[12].

Diagnosis and treatment

Psychological therapy depending on the severity and pattern of depression episodes over time may be recommended by healthcare professionals. ADs such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), as well as behavior, cognitive therapy, and interpersonal psychotherapy[13].

Antidepressant medication has complications, and health providers should think about their capacity to administer either intervention as well as their patients'

preferences. There are several treatment options available, including individual and/or group face-to-face psychological therapy provided by experts therapists. In minor depressive episodes, ADs would not be the first line of defense[13].

Depending on the severity and pattern of depression episodes over time, ADs may be advised as one of the therapeutic methods. On the other hand, ADs medication may have adverse drug reactions (ADRs). ADRs reduce people's quality of life, which leads to poor adherence to ADs, longer hospital stays, higher healthcare costs, poor therapeutic outcomes, physical morbidity, stigma and also death in the worst-case scenario. Psychiatrists must be familiar with the procedures for identifying and reporting ADRs, especially those that are new or unknown. Pharmacovigilance is a medical discipline based on these processes. This narrative review aims to provide an overview of depression, ADs, Antidepressant-related ADRs and the significance of pharmacovigilance. Articles were found using PubMed, Scopus, Google Scholar, MEDLINE and DergiPark databases. Firstly, we examined the title, then the abstract and finally the entire study.

Main Review Text Block

Antidepressants (ADs)

ADs are drugs that are prescribed to help people who are suffering from clinical depression. Also be used to treat diseases including GAD (generalized anxiety disorder), OCD (obsessive-compulsive disorder), and PTSD (post-traumatic stress disorder). ADs are sometimes prescribed to persons who suffer from long-term (chronic) pain[14].

Antidepressant (ADs) Types

There are a variety of different classes of ADs (Table 1).

Table 1. Antidepressant drug classes and mode of action ADRs reported

Classification	Mode of action	Drugs Examples	Reported ADRs
SSRIs	At the presynaptic neuronal membrane, selectively inhibit serotonin (5-HT) reuptake.	Citalopram, fluoxetine, paroxetine, escitalopram, and sertraline	i. sexual dysfunction, weight gain, and sleep disturbance[15]. ii. In pregnancy (neonatal seizures, premature birth, fetal and infant death)[16].
SNRIs	Both serotonin and norepinephrine reuptake inhibition; dopamine reuptake is mildly inhibited.	Duloxetine and venlafaxine	Blood pressure rises, tachycardia, anxiety, diaphoresis, and tremors [17].
MAOIs	Competitively inhibit monoamine oxidase; The reversibility and activity against MAOa and MAOb of the medicines in this class varies.	Tranylcypromine and phenelzine	Hypertensive crisis, persistent hypotension, insomnia, increased anxiety, agitation, and dry mouth [18].
SM	Serotonin reuptake inhibitor that also serves as a 5HT2 antagonist.	trazodone	Somnolence and fatigue[19].
NDRIS	Dopamine reuptake inhibition with some norepinephrine effects	bupropion	Headache, insomnia, nausea, and dry mouth[20].
NASSADs	Inhibition of the adrenergic alpha2-autoreceptors and alpha2-hetero-receptors additionally by inhibiting 5-HT2 and 5-HT3 receptors.	mirtazapine	Drowsiness, sedation, malaise, or lassitude[21].
TCAs	Norepinephrine and serotonin reuptake into presynaptic terminals inhibition.	Amitriptyline, imipramine, nortriptyline, desipramine	Constipation, dizziness, and xerostomia

*NDRIS (Dopamine norepinephrine reuptake inhibitors); SM (Serotonin modulators)

1. SSRIs (selective serotonin reuptake inhibitors)

The most commonly used antidepressant is SSRIs, which have minimal adverse effects on other classes. The most well-known SSRI is fluoxetine. Citalopram, escitalopram, paroxetine, and sertraline are some of the other SSRIs[22].

2. SNRIs (Serotonin-noradrenaline reuptake inhibitors)

SNRIs are ADs that are comparable to SSRIs but are intended to be more effective. However, there is no conclusive evidence that SNRIs are more successful in the treatment of depression. Duloxetine and venlafaxine are examples of SNRIs[23].

3. NASSADs (Noradrenaline and specific serotonergic ADs)

NASSADs may help some patients who simply cannot take SSRIs. NASSADs have similar ADRs to SSRIs but are less likely to cause sexual problems. Nevertheless, initially produce an increase in drowsiness[24].

4. TCAs (Tricyclic antidepressants)

TCAs are an older type of antidepressant that, due to the higher risk of overdose, is no longer proposed as the first line of therapy for depression. TCAs are used to treat several mental illnesses, including OCD and bipolar disorder[25]. TCAs include clomipramine, amitriptyline, dosulepin, lofepramine, and nortriptyline. Chronic nerve pain can be treated with TCAs such as amitriptyline[25].

5. SARIs (Serotonin antagonists and reuptake inhibitors)

SARIs are not typically recommended as a first-line antidepressant, although they may be taken if other ADs have failed or caused negative effects[26].

6. MAOIs (Monoamine oxidase inhibitors)

MAOIs are an antidepressant that is no longer commonly prescribed. They should only be given by a specialist because they have the potential to cause serious side effects. MAOIs include tranylcypromine, phenelzine, and isocarboxazid[18].

7. Other antidepressant treatments

Talking therapies, such as cognitive-behavior therapy (CBT), are another option for treating depression. ADs and CBT are commonly used to treat people with moderate to severe depression. ADs work fast to relieve symptoms, while CBT takes longer to address the causes of depression. Exercise has also been shown to help people who are suffering from mild depression[27].

Adverse drug reactions (ADRs)

Adverse drug responses (ADRs) are defined by the WHO as "an unpleasant and undesired response that occurs at levels typically used in humans for disease prophylaxis, diagnosis, or therapy, or the alteration of physiological function." ADRs are a documented source of morbidity and death in patients with depression, leading to increased hospitalization, healthcare expenses, problems, and decreased adherence[28]. ADRs are commonly observed in people with MDD, as per studies reported[29].

Antidepressant-related ADRs reported

According to the literature, ADRs occur at a rate of 5.01 to 21.45% among psychiatric outpatients[30]. Table 1 shows the ADRs reported in response to different antidepressant drugs. A larger number of ADRs was associated with SSRIs. Individuals taking SSRIs experienced more gastritis, sedation, weight gain, oral ulcers, restlessness, erectile dysfunction and tremor than those taking TCAs[31]. ADs discontinuation symptoms (also known as withdrawal symptoms) were originally described more than 40 years ago with imipramine, the first TCA[32]. Some of the major classes and the reported ADRs are discussed below.

SSRIs are thought to decrease seizure frequency as reported in the literature[33]. Open-label trials with citalopram revealed a reduction in seizure occurrence of 37 to 64% in patients with known epilepsy and

depression, as well as those without depression. Overdosing on SSRIs, on the other hand, has been linked to an increase in extracellular monoamine levels, which is assumed to be the cause of convulsions[34]. In a single toxicology unit, 14% of SSRI overdoses resulted in serotonin syndrome, 2.4% in a coma, and 1.9% in seizures. It's worth noting that escitalopram had a comparatively low GMS rate in this study, compared to the relatively high rate reported[35]. Erectile dysfunction and ejaculation delay are caused by overstimulation of 5-HT2 receptors in the spinal cord, whereas insomnia, anxiety, irritability, aggravation of depressive symptoms and decreased libido are caused by overstimulation of 5-HT2 receptors in the brain. In addition, antagonism of 5HT2c, H1 receptor, hyperprolactinemia, and a rise in serum leptin levels cause weight gain in antipsychotic drug users[36]. Drug–drug interactions (DDIs) were linked to almost 40% of ADRs observed with SSRIs. Most of them, especially in the elderly, occurred after taking psychotropics, antithrombotics, or diuretics. At least one probable DDI was found in 88% of SSRIs reports in the French Pharmacovigilance Database. This rate of occurrence matches that of other previously reported data[37].

SNRIs can be used to treat neuropathic pain, and they may have a lesser chance of experiencing adverse effects than TCAs. Nausea, vomiting, headache, sweating, increased BP (blood pressure), disorientation, and sleeplessness is some of the side effects of SNRIs[38]. There are some noradrenergic ADs on the market, most of which work by reducing neuronal noradrenaline re-uptake, while only a few medications are specific for this function. The detrimental effects of noradrenaline reuptake may be difficult to separate when medications have many functions, though the adverse effects of reboxetine. SNRIs are known to produce mild changes in blood pressure and heart rate, as well as perspiration and sleeplessness. Noradrenergic medications are less likely to cause sexual dysfunction than SSRIs, but they are more likely to cause urine hesitancy. There are still questions over whether ADs with various mechanisms of action are more likely to cause diabetes and hyponatremia[39]. Some people who are unable to take SSRIs may benefit from NASSADs. NASSADs have similar side effects to SSRIs but are less likely to cause sexual problems. However, at first, it causes drowsiness.

MAOIs (Monoamine oxidase inhibitors) are infrequently utilized in clinical practice for the treatment of depression. Because of their well-known adverse effects, some of which can be life-threatening, as well as the dangers of combining food and MAOIs. As a result, MAOIs should not be used in conjunction with other ADs or some prescription or nonprescription medications. Some major ADRs are associated with the MAOIs as listed below.

Hypertensive Crises, the onset of high BP, could result in a hypertensive trauma which was a serious issue with the form the major part of MAO inhibitors. When tranylcypromine produced cerebral bleeding and hypertensive crisis, researchers tried to figure out why. Following therapy with tranylcypromine, cheese consumption was linked to significant elevations in blood pressure. *Serotonin Syndrome,* MAO inhibitors cannot be used with other medicines that boost serotonin levels in synapses, such as SSRIs, because of the previously described hypertensive crisis caused by tyramine-containing foods. Excessive serotonin levels, hyper-stimulation of serotonin receptors, and the potentially lethal "serotonin syndrome" or serotonin poisoning may occur from such a combination[40]. *Drug-Drug Interactions (DDI),* is another factor to consider when using MAO inhibitors. Their metabolism, like that of many other drug classes, can affect different isoforms of cytochrome P450-dependent enzymes. Moclobemide, for example, appears to influence several isoenzymes (CYP2C19, CYP2D6, and CYP1A2). Patients who require cimetidine medication should have their moclobemide doses lowered since cimetidine inhibits moclobemide clearance[41].

Sertraline, paroxetine, and duloxetine (approximately 1 out of every 3 prescriptions), as well as venlafaxine and milnacipran, were less commonly involved with DDIs (around 1 of 4 prescriptions). It's difficult to pinpoint the pharmacological reasons that led to escitalopram and fluoxetine being classified as "risky" SSRIs[42]. Midazolam is a drug that is widely and safely used to control agitated poisoned patients in poisoning management and intensive care. TCAs are still prescribed and used in many countries despite the arrival of newer and safer ADs due to their cost-effectiveness[43]. The well-documented cardiovascular toxicity of these medicines is substantially to blame for the high morbidity and death associated with them[44]. TCA overdose patients who got midazolam for other reasons had a lower fatality rate and their hemodynamic indices were more near stable[44]. Similarly, the majority of ADRs are probably preventable[45]. While such adverse effects are endurable, special care should be taken to allow collaborative decision-making. Increasing the chances

of a person receiving effective treatment with the fewest ADRs is possible with the effort pledged to manage the ADRs[46]. All of the efforts in psychotherapy will eventually result in better outcomes and a decrease in ADRs. Antidepressant-related ADRs must be reported immediately, and the overall health sector must be engaged.

Antidepressants and the significant role of pharmacovigilance

ADs pharmacotherapy is the most frequent treatment choice for various mental illnesses. ADRs are common with most psychiatric medications[47]. Patients with depression frequently fail to respond to first-line medication and necessitate the use of multiple medications[48]. Some patients may require multiple drugs to be treated (polypharmacy), which can increase the risk of side effects and drug interactions[49]. Therefore, psychiatrists must understand the concepts and methods of pharmacovigilance[47]. The pharmacovigilance program tends to generate signals for rare and unknown ADRs. This can assist physicians in rational drug prescribing while keeping in mind drug-related ADRs[50,51]. A significant proportion of ADRs was observed to be preventable, it is critical to develop and implement strategies to avoid such ADRSs in the future by implementing the true nature of pharmacovigilance[52]. Rajkumar and Melvin classified the benefits of pharmacovigilance in psychiatry into four categories, such as; patient, clinician, pharmaceutical industry and regulatory authority-related benefits. The details are given below

Patient benefits: ADRs can be disturbing and problematic for patients, even if they are not life-threatening. Patients and physicians can gain trust by reporting these ADRs. Regular reporting behavior can help patients to comply with therapy and can also improve quality of life through earlier detection.

Clinician benefits: Pharmacovigilance can assist psychiatrists in identifying and managing potential ADRs. This is especially true for behavioral toxicity (drug-induced mania, drug-induced suicidality), which is best detected by clinicians/practitioners who interact with their patients regularly. In such cases, clinicians/physicians must be encouraged and rewarded for reporting ADRs.

Pharmaceutical industry benefits: The pharmaceutical industry's role in psychiatry has recently been called into question, with reports of serious ADRs being underreported and suppressed during clinical trials. Such ADRs can be identified at the earliest possible stage and necessary action taken before the drug is marketed if the principal investigators in such trials develop a "culture of pharmacovigilance". This will boost consumers' and healthcare professionals' confidence in pharmaceutical products.

Regulatory authority benefits: As previously stated, the majority of psychotropic drug trials published are short-term studies. Regulatory agencies may grant approval based on this information, but long-term negative consequences may not manifest themselves for a long time. Authorities may be able to remove or restrict the drug responsible if early "signal detection" of such events is possible[47].

Furthermore, it is critical to emphasize the importance of intensive ADR monitoring in psychiatric patients regularly[53]. Pharmacovigilance studies, as well as monitoring and evaluation of prescribing practices, are required to emphasize the rationality of medical care or to send a remedial massage to the prescriber and regulatory authorities[54]. All practicing physicians must engage in pharmacovigilance activities. Clinicians in the field of psychiatry, where long-term drug therapy is common are well-positioned to identify and report ADRs to regulatory agencies[47]. Previous research has highlighted the importance of clinical pharmacists monitoring ADRs in psychiatric settings regularly to detect and mitigate the risk posed by ADRs[53,55]. As a result, pharmacovigilance is not a "specialist" activity; it is a requirement for all those involved in the care of patients on medications, including doctors, nurses, pharmacists and paramedical staffs[56].

The updated knowledge of all healthcare professionals in psychiatry about ADRs produced by antidepressants drugs can help early detection of the adverse events. ADRs should also be reported as soon as possible so that appropriate steps can be taken to mitigate the patient's harm and prevent further damage[57]. Moreover, it is suggested that the use of modern technology in clinical practice, such as mobile apps and database software, may play an important role in psychiatric and other areas of medical treatment. The database contains information on patients' demographics, prescribed drugs, efficacy, and safety data and it could be a useful decision-making tool in clinical practice. Such information should be used in a variety of medical fields, as well as in future pharmacovigilance and pharmacoepidemiological studies[58,59].

Conclusion

Depression appears to be associated with an increased risk of developing ADRs. According to previously published studies, antidepressant medicines are linked to a variety of adverse effects. All healthcare providers should monitor ADRs in psychiatric patients on a frequent basis, according to this review. The establishment of unbiased functional organizations to monitor ADRs and receive reports notices regularly has been a major concern around the world. TUFAM (Turkish pharmacovigilance center), a unit of the Turkish Ministry of Health, was established in this regard and has been in operation in the field of pharmacovigilance since 2005. With the establishment of the Pharmacovigilance Program in Turkey, all psychiatrists should understand the key principles of this science and be able to apply them to the benefit of their patients and the healthcare community. As a result, a comprehensive pharmacovigilance system including all stakeholders (manufacturer, policymakers, healthcare professionals, academia, and patients) may be helpful to improve the quality of care and adherence among patients with depression and as well as for the reduction of healthcare costs.

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