

## MEDICATION-INDUCED PSYCHOTIC DISORDER. A REVIEW OF SELECTED DRUGS SIDE EFFECTS

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### SUMMARY

**Background:** Medication-induced psychotic disorder (MIPD) is a diagnostic term for a syndrome with symptoms such as hallucinations and delusions directly related to drug intake. The purpose of this review is to report and comment on the current knowledge about pathomechanisms, risk factors, symptoms, and treatment of MIPD caused by selected widely used medications.

**Methods:** PubMed, Scopus, and Google Scholar databases were searched for articles on MIPD published prior to January 2021 using search terms 'psychosis' OR 'psychotic disorder' AND 'side effects' combined with certain medications group. The initial search was then narrowed to medications with more pathomechanisms than only direct dopamine-inducing activity that are widely used by clinicians of various medical specialties.

**Results:** Steroids, antiepileptic drugs, antimalarial drugs, and antiretroviral drugs can induce psychosis with persecutory delusions and auditory hallucinations as the most frequently reported symptoms. Mood changes and anxiety may precede psychosis after steroids and antimalarials. Psychiatric history and female sex are risk factors for most of the MIPD. Treatment involves cessation of the suspected drug. Administration of atypical antipsychotic drugs may be helpful, although there is insufficient data to support this approach. The latter should be done with careful consideration of pharmacokinetic and pharmacodynamic interactions.

**Conclusions:** MIPD is a rare condition. The appearance of psychotic symptoms during systemic treatment may be associated with administered medications, psychiatric comorbidity, or be a part of the clinical picture of a certain disorder. Furthermore, sometimes it may be challenging to distinguish MIPD from delirium. Therefore, we consider that the key to proper management of MIPD is a thorough differential diagnosis.

**Key words:** steroids – anticonvulsants – antimalarials - anti-retroviral agents - substance-related disorders

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### INTRODUCTION

Psychosis can manifest with hallucinations, delusions, disorganized thought, disorganized behavior, and negative symptoms such as anhedonia, flat affect, isolation, or social withdrawal, which eventually lead to a loss of contact with reality. It is considered as a severe mental state requiring medical intervention (Gaebel & Zielasek 2015). Psychosis can be associated with a wide variety of illnesses. Primary psychotic disorder, substance/medication-induced psychotic disorder, psychosis associated with medical or neurological conditions should all be considered in the differential diagnosis (Calabrese & Khalili 2020).

There are several pathophysiological models of psychosis. The dopamine hypothesis arose from studies focused on substances that increase dopamine concentration and drugs that decrease dopamine levels (Carlsson et al. 1973, Lieberman et al. 1987). The conclusion was that positive symptoms (hallucinations and delusions) are mostly related to excess dopamine in the mesolimbic pathway. However, further research revealed that the connection between dopamine and psychosis is more complex. Increased striatal dopaminergic D2 receptors activation and decreased frontal D1 receptors activation may also explain cognitive deficits

and negative symptoms (Valton et al. 2017). The glutamate model refers to decreased N-methyl-D-aspartate (NMDA) glutamate receptors function that may also explain negative symptoms. The gamma-aminobutyric acid (GABA) hypothesis pointed to the role of reduced GABAergic inhibition in the pathogenesis of schizophrenia (Howes et al. 2015).

The Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association. 2013) distinguishes substance/medication-induced psychotic disorder. To diagnose the disease, certain criteria must be met. First of all, the presence of delusions or/and hallucinations, which must develop during treatment or within a month of substance withdrawal. The condition cannot be better explained by psychotic disorder not related to medication or substance. Medication should be etiologically related to the disturbance. Patients' mental state must cause clinically significant distress or functional impairment. Symptoms cannot occur exclusively during the course of a delirium. Reality assessment is distorted, a patient has no insight and is unaware that the altered perception is substance-induced.

The aim of this article is to summarize the available knowledge about the psychotic side effects of selected medications. The authors chose these drugs because of

their wide application in many branches of medicine, proven psychotic effects, and complex pathomechanisms of inducing psychosis. They are used in the treatment of many conditions, including disorders with the psychotic course. Therefore, many specialists may encounter medication-induced psychosis in their practice and may deal with difficult differential diagnosis. Thus, there is a need for knowledge to be provided with the correct medical approach.

## METHODS

PubMed, Scopus, and Google Scholar databases were searched for articles on MIPD until January 2021. We used a query containing 'psychosis' OR 'psychotic disorder' AND 'side effects' combined with each medication group i.e. steroids, corticosteroids, antiepileptic drugs, anticonvulsants, antimalarial drugs, antiretroviral drugs, and with particular drugs in each group. We focused on medications that have several mechanisms of inducing psychosis or have indirect dopamine path activation. We excluded articles describing overdoses. We performed no statistical calculations.

## RESULTS

### Steroids

Steroids can cause several psychiatric symptoms. The most common are mania (35%) and depressive symptoms (28%), followed by mania and depression (12%), delirium (12%), and psychosis (11%) (Sirois 2003). Publications qualify 'mania and depression' as a separate condition. Without detailed information we may only suspect that this actually is a description of a mixed episode in the course of bipolar disorder. Psychiatric disorders during corticosteroid treatment may appear 3-4 days after treatment initiation. Symptoms usually resolve within a week after therapy cessation (Sirois 2003, Janes et al. 2019).

The first report which documented psychotic symptoms associated with steroids was published in 1950 (Rome & Braceland 1950). Research show that steroid-induced psychosis usually lasts around a week (Sirois 2003, Janes et al. 2019). However, the estimated time of onset of psychotic symptoms is not established. In most cases, the psychotic disorder occurs during systemic treatment, but such symptoms were also present during local steroid administration (Janes et al. 2019). Psychotic adverse effects may develop rapidly following exposure to even low doses, with oral, epidural, or intra-articular administration (Ross & Cetas) with the usual presentation of persecutory delusions, auditory hallucinations, disorganized behavior, and thought impairment (Sirois 2003, Bhangle et al. 2013, Janes et al. 2019). Mood changes may precede psychotic symptoms (Kim et al. 2020). In pediatric cases, steroid-induced psychosis manifested with auditory hallucinations, ideas of reference, loosening of association, and incoherent speech (Kim et al. 2020).

Dosage is the most significant factor of developing psychiatric effects during steroid treatment (Brown et al. 2002). Daily use of more than 40mg prednisone increases the risk of psychotic episodes, which was confirmed by the Boston Collaborative Drug surveillance program which analyzed psychiatric reactions related to prednisone treatment and its dosage. Psychiatric symptoms were present in 1.3% of patients receiving 40 mg or less of prednisone per day, 4.6% of patients receiving 41-80 mg per day, and 18.4% of patients who received more than 80 mg per day (The Boston Collaborative Drug Surveillance Program 1972). The dosage was not related to the severity or duration of psychiatric symptoms (Sirois 2003). Several studies show that women may be more vulnerable to psychiatric side effects than men. The higher risk could not be explained by a higher occurrence of conditions requiring steroid treatment among women (Ross & Cetas 2012, Lewis & Smith 1983). Most steroid-induced psychosis cases were reported as a side effect of prednisone treatment, which may be due to its more frequent administrations. Such effects also occurred during methylprednisolone, dexamethasone, and ACTH treatment (Bhangle et al. 2013). According to research, previous psychotic episodes or psychiatric history are not reliable risk factors for developing steroid-induced psychosis (Ross et al. 2003, Bhangle et al. 2013). A disturbed or normal course of previous steroid treatment is also not applicable for predicting psychiatric side effects during subsequent steroid use (Sirois 2003). Caution is recommended in elderly patients where, due to a higher incidence of renal and liver dysfunction, steroid plasma concentration can be higher. Additionally, frequent polypharmacy in this group of patients may result in steroid treatment interactions leading to a greater risk of steroid adverse effects (Dubovsky et al. 2012). Steroids are metabolized by CYP3A4. Drugs that inhibit this cytochrome may elevate steroid concentration. This should be taken into account when CYP3A4 inhibitors, such as ketoconazole, contraceptives, or clarithromycin, are prescribed with steroids (Sirois 2003, Dubovsky et al. 2012). Lower doses should be considered also in the case of patients with liver or renal failure (Dubovsky et al. 2012, Bhangle et al. 2013). Another group of patients with a greater risk of psychiatric steroid-induced side effects are those affected with systemic lupus erythematosus (SLE). Additionally, lupus may have a psychotic course, with hallucinations and delusions. Therefore, in some cases, differential diagnosis is difficult since SLE is usually treated with steroids (Bhangle et al. 2013).

A possible mechanism of steroid-induced psychosis is hypothalamic-pituitary-adrenal (HPA) axis suppression and altered levels of neurotransmitters. It leads to increased dopamine activity in the brain, which can contribute to psychotic reactions. While the exact pathophysiology of steroid-induced psychosis is not clearly elucidated, the HPA axis model is usually proposed (Sirois 2003, Bhangle et al. 2013, Janes et al. 2019).

Treatment of steroid psychosis is based mainly on cessation of steroids or decreasing its dosage under the equivalence of 40 mg of prednisone. When steroid withdrawal is not possible, or symptoms are severe, it may be necessary to use antipsychotic treatment. Atypical antipsychotic drugs, such as olanzapine and risperidone are recommended as first-line pharmacotherapy. Tricyclic antidepressants and neuroleptics with strong anticholinergic activity should be avoided in patients with steroid-induced psychiatric symptoms as they may exacerbate psychiatric adverse effects (Ross & Cetas). This is especially dangerous in case of misdiagnosing delirium as a psychotic episode. The strong cholinolytic activity of these drugs is a known sole cause of consciousness impairment episodes (Woolf et al. 2007). Administered to already delirious patient, they may lead to further worsening mental and somatic condition, leading to a direct threat to one's life.

Reports have been published describing lithium prophylaxis in the management of psychotic reactions associated with steroid treatment (Falk et al. 1979, Goggans et al. 1983). However, its beneficial effects were observed mainly in subjects with psychotic symptoms during mood episodes, which suggests that the basis of the condition were affective and schizoaffective disorders. In these cases, we consider a mood-stabilizing activity of lithium as more probable than an antipsychotic one. Therefore, lithium prophylaxis should not be considered the first choice in clear-cut psychosis.

### Antiepileptic drugs

Epilepsy is known to increase vulnerability to mental disorders and affected patients often have psychiatric comorbidities. They suffer from depression, anxiety, and psychotic disorders (Clarke et al. 2012, Lin et al. 2012). Sometimes psychiatric conditions precede the onset of epilepsy (Hesdorffer et al. 2012). The selection of suitable antiepileptic drugs (AEDs) may be difficult, especially in patients who already have psychiatric symptoms (Brodie et al. 2016).

While the administration of some AED's may be beneficial due to their mood-stabilizing effect and the possible role in the augmentation of anti-depressant or antipsychotic treatment, they may also cause a variety of psychiatric side effects (Alper et al. 2007, Cavanna et al. 2010, Piedad et al. 2012). These symptoms may influence patients' quality of life even more than seizures themselves (Cavanna et al. 2010). Psychotic symptoms seem to be less common than mood disturbances, but they are reported in clinical trials. The diagnosis of antiepileptic drug-induced psychosis (ADIP) can be challenging. It needs to be distinguished from other psychotic states related to seizures, such as perictal psychosis (including pre-ictal, ictal, and post-ictal psychosis), forced normalization psychosis, and interictal psychosis (Agrawal & Mula 2019). Furthermore, patients can have a comorbid psychotic disorder or substance-induced psychosis caused by other medications or substances (Chen et al. 2016).

Psychosis is not common in patients with epilepsy, but it is a serious condition that demands proper treatment. A systematic review and meta-analysis estimate the prevalence of the psychotic disorder in this group of patients at 5.6%. A higher prevalence (7%) is reported in patients with temporal lobe epilepsy (Clancy et al. 2014). Studies also show a bidirectional relation between schizophrenia and epilepsy. Patients with schizophrenia have a higher risk of epilepsy than the general population. On the other hand, people with epilepsy have an elevated risk of developing schizophrenia (Wotton & Goldacre 2012).

Psychotic symptoms are reported after levetiracetam, lamotrigine, tiagabine, vigabatrin, and zonisamide treatment (Piedad et al. 2012, Stephen et al. 2017, Pinckaers et al. 2019). Few studies investigated psychotic reactions related to AEDs. A retrospective cohort study from Royal Melbourne Hospital analyzed records of 2630 patients with epilepsy. In this group, 98 patients experienced psychosis, with 14 of them being diagnosed with ADIP (Chen et al. 2016). It should be emphasized, however, that this study included a specific group of patients with mostly atypical and severe course of an illness, who supposedly can be more susceptible to psychiatric side effects. Due to hospitalization and uncontrolled seizures they were also closely monitored and thoroughly diagnosed. This may have led to a selection bias with an overrepresentation of psychotic symptoms that does not reflect their prevalence in the population of patients with epilepsy. Furthermore, out of the 14 patients diagnosed with ADIP, 3 patients were experiencing only visual hallucinations and disorganized behavior, which may point to a misdiagnosis of delirium. Additionally, several patients had other conditions predisposing to psychosis, such as brain tumors, neurological surgery history, or temporal lobe epilepsy. In this case, it is difficult to determine the exact cause of psychotic symptoms.

In another study, Chinese patients were assessed to explore the risk factors for antiepileptic drug-induced adverse psychotropic effects. Out of 1001 patients with AEDs adverse psychiatric effects, 47 developed psychotic symptoms (Du et al. 2019), mainly hallucinations. However, there is no information on their sensory modality, which may be crucial in the verification of the correctness of the diagnosis. For instance, as mentioned before, visual hallucinations are frequently present in delirium but also may be part of the clinical picture of epilepsy itself and are unlikely to be present in schizophrenia-like psychoses.

Studies show that psychotic disorder comorbidities may be a risk factor for developing psychiatric side effects of AEDs (Stephen et al. 2017, Chen et al. 2018, Du et al. 2019). Other suggested risk factors for ADIP and psychiatric side effects, in general, include female sex (Chen et al. 2016, Du et al. 2019, Pinckaers et al. 2019), the focal onset of seizures (Chen et al. 2016, Stephen et al. 2017), levetiracetam therapy (Chen et al. 2016, 2018, Stephen et al. 2017, Pinckaers et al. 2019),

and family or personal history of psychiatric disorders (Du et al. 2019). While the data is still scarce, recognizing these factors may provide some assistance in choosing the best antiepileptic therapy.

Guidance for the treatment of psychotic symptoms in epilepsy is scant in the literature. Clinicians should pay attention to interactions and seizure risk when choosing an antipsychotic drug. AEDs, such as phenytoin or carbamazepine, by inducing CYP3A4 may accelerate the metabolism of antipsychotics, especially quetiapine. On the other hand, antipsychotic drugs generally do not affect the blood levels of AEDs (Agrawal & Mula 2019). It is also important to avoid additive side effects during antipsychotic treatment. For example, the combination of clozapine and carbamazepine is contraindicated due to the additive effect of agranulocytosis. Clozapine is also associated with the highest risk of seizures among all antipsychotics, while risperidone and other strong antipsychotics (efficacy within a few milligram dosing range) with the lowest (Alper et al. 2007). According to Agrawal and Mula with its safety profile (low risk of seizures and interactions), risperidone can be considered a first-line treatment for psychotic patients with epilepsy. The authors also point out that more research is needed to clarify guidelines for treating psychotic symptoms in patients with epilepsy (Agrawal & Mula 2019).

### Antimalarial drugs

Psychotic adverse effects of antimalarial drugs seem to be rare. However, some reports describe psychotic disorders induced by chloroquine, hydroxychloroquine, and mefloquine (Alisky et al. 2006, Bogaczewicz & Sobów 2017, Sato et al. 2020, Hamm & Rosenthal 2020). According to a report based on data from the FDA Adverse Reporting System, chloroquine-induced psychosis is a rare phenomenon (2.3%) in comparison to other neuropsychiatric adverse events (Sato et al. 2020).

One of the studies on the subject described 520 subjects (out of 4.336) who developed neuropsychiatric side effects after exposition to chloroquine and mefloquine. A statistically significant association was demonstrated between chloroquine use and the occurrence of hallucinations (4.6%), as well as between mefloquine and neuropsychiatric events, including psychosis (6.0%) (Sato et al. 2020). The main limitation of the study is the use of self-reported data, which can result in over or under-reporting of adverse effects.

Another study results (based on a population of 35 370) suggest that first-time acute psychosis may be more common during exposure to mefloquine than other antimalarial drugs. However, according to this publication, the risk of developing psychosis during mefloquine treatment is still low. Out of the study group, 580 patients with severe psychiatric symptoms were distinguished. Among them, 16 were diagnosed with a first-time psychotic episode. The study excluded patients on

long-term antimalarial treatment, such as rheumatoid conditions (Meier et al. 2004). With this limitation, we may assume that the number of patients with antimalarial drug-induced psychosis does not reflect the population. On the other hand, some studies reported a negative association of rheumatoid arthritis with psychosis as opposed to other autoimmune diseases (Jeppesen & Benros 2019).

Various psychotic symptoms are reported during antimalarial treatment including suspiciousness, delusions, auditory, visual, and tactile hallucinations, ideas of reference, and even catatonic state (Das et al. 2014, Bogaczewicz & Sobów 2017, Sato et al. 2020). Additionally, the U.S. Drug label distinguished acute anxiety, depression, restlessness, or confusion as symptoms that may precede other, more serious, psychiatric adverse effects. During prophylactic use, when such symptoms occur, drugs should be discontinued and substituted by other medications (Nevin & Byrd 2016). Dizziness, insomnia, generalized anxiety, or violent behavior can also precede a psychotic episode (Tran et al. 2006, Mascolo et al. 2018).

A single case report on the exacerbation of bipolar disorder with psychotic features after exposure to chloroquine describes a patient who experienced two episodes triggered by the drug. Firstly, depression with psychotic symptoms occurred. Secondly, chloroquine caused agitation, visual and auditory hallucinations in the course of a manic episode. Medication was switched to hydroxychloroquine, quetiapine, and lamotrigine were prescribed. During a one-year follow-up no psychiatric symptoms occurred, mood disorder was in remission (Bogaczewicz et al. 2014). However, it is worth mentioning that there are also cases of hydroxychloroquine-induced psychotic effects (Das et al. 2014, Gonzalez-Nieto & Costa-Juan 2015).

Risk factors for experiencing psychiatric effects during chloroquine or hydroxychloroquine treatment may include psychiatric history, female sex, family history, low body weight, concomitant administration of steroids, or alcohol intake (Meier et al. 2004, Mascolo et al. 2018). Additionally, the co-administration of CYP3A4 inhibitors can prolong the chloroquine or hydroxychloroquine half-life. This may increase the risk of developing psychiatric side effects (Mascolo et al. 2018). One hypothesis states that co-administration of drugs potentiating dopaminergic activity (such as levodopa, carbidopa, or bupropion) could increase the incidence of psychosis (Alisky et al. 2006).

As mentioned earlier, rheumatic diseases, such as SLE, can cause neuropsychiatric symptoms, including psychotic episodes. These conditions are often treated with antimalarial drugs, which may make the differential diagnosis of psychotic disorders more difficult (Joaquim & Appenzeller 2015), especially if we consider that these patients also frequently require steroid treatment (Bogaczewicz et al. 2014).

There are various reports on the duration of antimalarial-induced psychiatric symptoms. Timespan

ranges from several hours to a month, but usually, symptoms resolve within one week following cessation of the drug (Das et al. 2014, Bogaczewicz et al. 2016, Bogaczewicz & Sobów 2017). The long half-lives of chloroquine (20-60 days), hydroxychloroquine (40-50 days), mefloquine (13-24 days) (Drugs | FDA 2011) may result in sustained psychiatric side effects for up to several weeks after discontinuation of treatment (Sato et al. 2020). In 2013, the U.S. Food and Drug Administration reported that mefloquine-induced neuropsychiatric adverse reactions could persist for months or years after mefloquine cessation (Nevin & Byrd 2016).

Antimalarial drugs have the ability to cross the blood-brain barrier (BBB), which results in their brain concentration being higher than the plasma level (Dow et al. 2011, Mascolo et al. 2018, Sato et al. 2020). This feature is important in terms of inducing psychotic side effects. There are several proposed pathomechanisms of antimalarials-induced psychotic episodes. One of them is dopaminergic pathway activation. Chloroquine can prevent the down-regulation of dopamine receptors (Bogaczewicz et al. 2014). Mefloquine can additionally potentiate dopamine (Alisky et al. 2006). Some data report that a possible mechanism of chloroquine-induced psychosis is interference with the cholinergic system, with chloroquine acting as a muscarinic antagonist (Alisky et al. 2006, Bogaczewicz & Sobów 2017). However, this is rather a characteristic of the anticholinergic syndrome, which may lead to an impairment of consciousness with disorientation, insomnia, agitation, and visual hallucinations among other psychiatric symptoms (Brown et al. 2004). Therefore, delirium syndrome should always be excluded before starting antipsychotic treatment. Additionally, the hypothesis that mefloquine may cause psychiatric symptoms by influence on retinoid metabolism was proposed (Mawson 2013). Another significant mechanism is P-glycoprotein inhibition. P-glycoprotein is responsible for pumping drugs out of the central nervous system. Mefloquine and chloroquine bind to the protein and inhibit its action. This may lead to increased levels or even supratherapeutic concentration of antimalarials in the brain (Alisky et al. 2006, Das et al. 2014). Additionally, mefloquine-induced psychosis may emerge from disrupting neuronal calcium homeostasis and inhibition of gap junction formation (Alisky et al. 2006). This may disrupt the work of neurons and cause psychiatric symptoms. Disturbance of calcium homeostasis was already reported as a cause of psychotic symptoms (Nagy et al. 2020).

There are no guidelines for the treatment of antimalarial drugs-induced psychosis. In the reported cases, patients were treated with antipsychotics such as quetiapine, risperidone, or olanzapine. Moreover, the antimalarial drug was discontinued in the event of psychotic symptoms (Tran et al. 2006, Bogaczewicz et al. 2014, Das et al. 2014, Mascolo et al. 2018).

## Antiretroviral drugs

Antiretroviral therapy (ART) is associated with psychotic episodes. The occurrence and frequency of these side effects vary among the classes of antiretroviral drugs (ARVs) and individual drugs in each class (Foster et al. 2003, Abers et al. 2014, Lanman et al. 2019). Current ART clinical guidelines recommend combined ART for the treatment of HIV infection (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV 2019). People living with HIV require life-long therapy. Therefore, the exposure to side effects and toxicity of ARVs is prolonged (Lanman et al. 2019).

HIV crosses BBB and is detected in cerebrospinal fluid (CSF). Most ARVs penetrate BBB and reduce the HIV reservoir in the CNS. However, CNS exposure to ART can be associated with a higher risk of neurotoxicity. Therefore, it can result in an elevated risk of neuropsychiatric adverse events (Lanman et al. 2019).

The primary mechanism of nucleoside reverse transcriptase inhibitors (NRTIs) CNS toxicity is mitochondrial polymerase inhibition and oxidative stress (Nooka & Ghorpade 2018) and it is postulated, that abnormalities in mitochondrial function and structure are associated with schizophrenia (Roberts 2021). Among non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz is the most CNS toxic. Pathomechanism of its toxicity is similar to NRTIs: oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress. Efavirenz is associated with long-term cognitive impairment. Compared to this drug, other ARVs from NNRTIs class are less studied (Lanman et al. 2019). Ritonavir is the most neurotoxic among protease inhibitors (PIs). However, it is also used as a pharmacokinetic (PK) enhancer in low doses. It can reduce ritonavir-induced adverse effects. Cobicistat (another PK enhancer) was not reported to cause CNS toxicity. Additionally, entry inhibitors seem to be least neurotoxic among ARVs (Lanman et al. 2019).

HIV infection itself also affects the mental state of the patient. Psychotic episodes caused by the virus are reported. The disease can also exacerbate existing psychiatric disorders. It may be difficult to distinguish whether the symptoms are caused by medications or the course of the illness. Additionally, HIV infection is more prevalent among people with severe mental illnesses, such as schizophrenia, schizoaffective disorder, and other psychosis (Bauer-Staeb et al. 2017).

Various psychotic symptoms are reported during ART including persecutory delusions, grandiose delusions, visual hallucinations, auditory hallucinations, catatonic state, agitation, and irritation (Foster et al. 2003). Psychotic symptoms were observed in patients treated with zidovudine (Maxwell et al. 1988, Foster et al. 2003, Abers et al. 2014), abacavir (Foster et al. 2003, Abers et al. 2014), nevirapine (Wise et al. 2002), and, most frequently, with efavirenz (de la Garza et al. 2001, Poulsen & Lublin 2003, R. et al. 2003, Abers et al. 2014, Hinsch et al. 2014).

Risk factors for the development of psychiatric side effects during ART are not well recognized. There are assumptions, but extensive research is needed to confirm them. History of psychiatric, including psychotic, disorders may increase the risk of efavirenz-induced psychotic symptoms (Abers et al. 2014). Efavirenz is metabolized with CYP2B6 and CYP3A4. Inhibitors of those cytochromes increase efavirenz concentration. This can result in greater CNS toxicity and an increased risk of psychotic symptoms (Cavalcante et al. 2010, Abers et al. 2014, Hinsch et al. 2014).

There is little information about the treatment of ARVs-induced psychosis. Cessation of suspected drugs or/and introduction of antipsychotic drugs may be effective (Foster et al. 2003). Clinicians should exercise caution as there are interactions between antipsychotics and ARVs (Penzak et al. 1999). Efavirenz and nevirapine can lower aripiprazole, brexpiprazole, cariprazine, lurasidone, primavaserin, pimozide, and quetiapine concentrations. Efavirenz co-administrated with olanzapine may decrease olanzapine concentration. Due to this fact, the therapeutic effectiveness of antipsychotics should be monitored if prescribed with listed ARVs (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV 2019).

## CONCLUSIONS

Clinicians should pay attention to the potential psychotic adverse effects of prescribed medications. Psychotic side effects of presented drugs are relatively infrequent. However, their occurrence may significantly complicate the treatment and cause severe psychological distress. Early diagnosis and proper management of psychotic events may increase the quality of the treatment and decrease the length of hospital stay. Differential diagnosis is difficult because psychotic symptoms may also appear in the course of base illnesses or as a comorbidity. Furthermore, delirium symptoms frequently resemble psychosis. Therefore, consciousness impairment always has to be excluded before starting antipsychotic treatment. An overlook here may have serious implications not only influencing treatment itself but posing a potential threat to the health or life of the patients. As such differential diagnosis may be challenging, psychiatric consultation should be performed if available. Antipsychotic medications are commonly administrated in patients with MIPD as the first line of treatment. However, in the absence of solid scientific evidence, their use is based primarily on common sense.

With data on identification and duration of psychotic adverse effects, a focus on risk factors could help in choosing proper medication and decreasing the prevalence of drug-associated psychotic disorders. Further interdisciplinary research focusing on correct diagnosis, treatment, and adequate management of medication-induced psychosis is required.

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