

Neuropsychiatric Adverse Effects of Non-Psychotropic Drugs

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ABSTRACT

The adverse effects of psychotropic medications and psychoactive substances have been well studied and recognised. Non-psychotropic drugs that are regularly prescribed for various medical disorders are known to have similar neuropsychiatric adverse effects which may range from anxiety to psychosis. Physicians should be aware of neuropsychiatric adverse effects of prescribed drugs so that they can educate patients and caregivers regarding the adverse effects and develop measures to minimize risk.

Keywords: Neuropsychiatric; Adverse effects; Non-psychotropics

ABOUT THE STUDY

Psychiatric ADRs (Adverse Drug Reactions) are not uncommon and can be due to a wide range of non-psychotropic drugs that are commonly prescribed in medical and surgical specialties. Individuals with no prior psychiatric history, as well as those with previous or current psychiatric illnesses, can develop psychiatric ADRs [1,2].

An intervention related to the use of a medicinal product resulting in a significant harmful or unpleasant reaction is defined as an Adverse Drug Reaction (ADR). ADRs typically indicate a risk from further administration and warrant prevention, or specific treatment, or change in dosing regimen, or withdrawal of the drug [3].

For three reasons, knowledge regarding neuropsychiatric ADRs of non-psychotropic drugs seems vital. First, awareness of adverse effects of non-psychotropic drugs is important for efficient and safe pharmacotherapy, which helps in preventing major psychiatric disturbances due to medication use and also in assisting clinicians in determining the "cost," in terms of psychological changes, of a drug treatment for somatic complaints can or cannot be given. Second, understanding the psychotropic effects of primarily somatotropic drugs can aid in the development of hypotheses about multifactorial mechanisms of drug action that include psychological and physiological components as well as their interactions. Thus, research on neuropsychiatric ADRs of non-psychiatric drugs can help to determine the psychosomatic relationships that underpin drug

action in general. It can also identify distinct pathways of somatopsychic information transmission and processing. Third, psychotropic effects, which are undesirable adverse effects of non-psychotropics, could lead to the administration of psychopharmacological agents to deal with psychiatric disorders [4].

Psychiatric ADRs of drugs are often understudied in clinical research as they are rare events in clinical practice that are grouped together by research instruments as 'psychiatric effects' [5]. This article describes neuropsychiatric adverse effects induced by commonly used non-psychotropic drugs, with emphasis on herbal remedies.

Overview of neuropsychiatric adverse effects

Herbal supplements and medications are often involved in the development of neuropsychiatric symptoms [6]. PSEs (Psychiatric Side Effects) have a similar clinical presentation to spontaneous psychiatric disorders. PSEs can occur at normal doses, during intoxication, or in the days following a treatment's discontinuation [7].

Medications used in the management of non-psychiatric disorders can modify neurotransmitter systems. The action of these medications can have a direct influence on neurotransmitters similar to psychotropic medications. They may hyper-activate the hypothalamus-pituitary-adrenal axis and elevate the levels of cytokines such as IL-1 β , IL-6, γ -IFN, positive acute-phase proteins [8].

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Disease states, drug interactions and hepatic enzyme polymorphisms are the leading causes of side effects. Many drugs interfere with one or more hepatic metabolism pathways, especially the Cytochrome P450 enzyme system [8].

The Adverse Drug Reaction Probability Scale, or The Naranjo Algorithm, is a 10-item probability scale by which determines the relationship between an identified unanticipated clinical event and a drug [9]. It is the most commonly used Adverse Drug Reaction instrument in the literature and in clinical settings (Table 1) [10].

Neuropsychiatric side effects and drugs implied	
Symptoms	Drugs
Anxiety	Antivirals, clonidine, nitrates, penicillin, steroids.
Cognitive dysfunction	Anticholinergics, anticonvulsants, antidepressants, corticosteroids, H2 blockers, NSAIDs.
Depression	Antiretrovirals, β blockers, clonidine, GnRH agonists, H2 blockers, IFNs, steroids.
Delirium	ACE inhibitors, antibiotics, anticholinergics, β blockers, H2 blockers, steroids.
Insomnia	β blockers [11], clonidine, loop diuretics, proton pump inhibitors, quinolones, salbutamol, skeletal muscle relaxants, steroids.
Manic reaction	Baclofen, chloroquine, Dopamine agonists, H2 blockers, steroids, sympathomimetics, thyroxin, TNF α inhibitors [12].
Psychosis	Clonidine, H2 blockers, proton pump inhibitors, quinolones, salbutamol, steroids.
Sexual dysfunction	Anticonvulsants, antihistamines, benzodiazepines [13], β -blockers, diuretics, muscle relaxants, OCPs [14].
Seizures	Antimalarials, CNS stimulants, cyclosporine, fluoroquinolones, systemic steroids.
Suicidal ideation and suicidality	Antiretrovirals, antifungals, cycloserine, fluoroquinolones, IFNs, Isotretinoin [15], nitrates.
Substance addiction	Cough syrups, dextromethorphan, ketamine, loperamide, steroids.

ACE: AngiotensinConverting Enzyme; CNS: Central Nervous System; GnRH: GonadotropinReleasing Hormone; IFN: Interferon; NSAID: Nonsteroidal AntiInflammatory Drugs; OCPs: Oral Contraceptive Pills; TNF: Tumour Necrosis Factor.

Table 1: Outlines the various psychiatric symptoms and the drugs implicated [1].

Herbal remedies

Patients might use several herbal products, either alone or in combination with allopathic medicine for various physical and psychiatric disorders [16]. In western countries, particularly Europe and the United States, herbal products are considered the best option as complementary medicine. Annual sales of dietary herbal remedies are up 6.8% year over year in the United States. Furthermore, China and India are the top exporters, with Germany, Hong Kong, Japan, and the United States being the leading importers [17].

The two main mechanisms by which herbal remedies may have unfavorable effects on mental health are: (i) interactions between psychiatric medications and herbs and/or (ii) intrinsic toxicity of the herbs [18].

Toxicity of herbal ingredients, adulteration and contamination, and herb-drug interactions all contribute to misuse. Various case reports reported various adverse effects such as cerebral arteritis, cerebral oedema, confusion, coma, delirium, encephalopathy, hallucinations, intracerebral haemorrhage and other cerebrovascular accidents, movement disorders, mood disorders, muscle weakness, paraesthesia, and seizures. Few deaths have been reported [17,19] (Table 2).

Traditional uses and neuropsychiatric adverse effects of herbal remedies

Herbal remedies	Traditional use	Side effects
<i>Datura stramonium</i> (Jimson weed)	Asthma, muscle spasm, Parkinson's disease, whooping cough	Ataxia, blurred vision, disorientation, other cholinergic signs.
<i>Ephedra sinica</i> (Ma huang)	CNS-stimulant, asthma, fever	Anxiety, confusion, insomnia, Psychosis.
<i>Eucalyptus</i> sp.	Nasal congestion	Delirium.
<i>Ginkgo biloba</i> L.	Angina, Asthma, hypertension, tinnitus	Headache, dizziness.
<i>Mentha pulegium</i> L. (Pennyroyale)	Abortifacient, tumours	Confusion, hallucinations.
<i>Panax ginseng</i>	Promotes health	Insomnia, mania.
<i>Passiflora incarnata</i> L.(Passion flower)	Neuralgia, seizures, hysteria, insomnia	Nausea, drowsiness.
<i>Paullinia cupana</i> (Guarana)	CNS stimulant	Symptoms of caffeine intoxication, manic

		reaction, insomnia, somnolence, asthenia, fatigue, anxiety, impaired concentration.
<i>Pausinystalia yohimbe</i>	Erectile dysfunction	Anxiety.
<i>Piper methysticum</i> (Kava)	Urogenital infections, relaxation	Choreoathetosis, ataxia, tremors, sedation.
St John's wort	Wound healing, diuretic, pain, melancholy, etc	Anxiety, headache, sedation, mania.

Table 2: Outlines some of the herbal remedies with their uses and neuropsychiatric adverse effects [17,18,20,21].

Assessment and management

Neuropsychiatric ADRs can be difficult to diagnose. Depressive, anxious, or psychotic ADRs meet the majority of DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria for the corresponding spontaneous syndromes. Therefore, until proven otherwise, almost any psychiatric symptom or syndrome could be considered a possible ADR [7].

The first-line tools for diagnosing neuropsychiatric ADRs are the history and chronology of administration of medication. A history with a positive exposure, positive dechallenge (disappearance of an adverse effect after the drug has been stopped), and positive rechallenge (occurrence of an adverse effect after the drug has been restarted), indicates a high probability of association between a prescribed medication and a psychiatric symptom [7].

Investigations can help with diagnosis, establish baselines for organ function, and provide a means for monitoring what happens after changes in therapy [22]. Monitoring plasma concentrations of suspected medications is generally the most useful complementary examination for neuropsychiatric ADRs investigation (Table 3).

Key points to consider for detection of neuropsychiatric ADRs [7]
Plasma concentration measurements.
Previous psychiatric history.
Dates of occurrence of psychiatric symptoms suspected of being side effects.
Dates of medication exposure, dechallenge, and rechallenge.
If polypharmacy is given, dates of introduction or discontinuation of other drugs.
Dates of factors worsening existing comorbidities.

Table 3: Outlines the points to consider for the assessment of neuropsychiatric ADRs [7].

Psychoeducation may be considered for both the patient and family members. The aim is to educate the patient and their family about their psychiatric illness. Psychoeducation helps the patient to make precise attributions and conclusions regarding their psychological changes.

If an equally effective and safer alternative exists, ideally the 'offending' drug is switched to the alternative. If no safer alternatives exist, and pharmacotherapy for primary illness is necessary, then psychotropics can be used for management [16]. It is preferable to start the psychotropics at a minimal effective dose and increase the dose gradually based on the patient's response [1].

CONCLUSION

The key to ensuring an accurate diagnosis of a psychiatric adverse effect is by taking an accurate history of psychiatric symptoms that may be attributed to the drug and working out the timeline of symptoms. Since spontaneous psychiatric diseases often necessitate long-term treatment, the correct diagnosis of a neuropsychiatric ADR can spare the patient from distress, stigma, and other costs of gratuitous long-term psychiatric treatment. Pharmacotherapy for primary medical conditions can be modified by either changing drug intake timing or by reducing the dosage of the drug which are associated with psychiatric adverse effects, and by discontinuing unnecessary or non-essential drugs to avoid interactions. In the case of severe or life-threatening symptoms, major changes such as medication discontinuation or switching may be required.

CONFLICT OF INTEREST

There are no conflicts of interest.

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