Psychiatric effects of drugs for other disorders

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Abstract

Psychiatric adverse drug reactions (ADRs) have been reported with a diverse range of medicines used in the treatment of physical illness. Whereas some are mild (such as transient sleep disturbances), others are severe (such as psychosis) and warrant discontinuation of the suspected causal agents. Some reactions are predictable, while others are unpredictable. The mechanism by which they are mediated is often unclear. It is essential that serious psychiatric ADRs observed during routine clinical practice be reported via the UK's Yellow Card reporting scheme as many are relatively uncommon and may only be detected through postmarketing surveillance in the wider population. Patients have reported finding symptoms of psychiatric ADRs extremely distressing and sometimes frightening, and may be hesitant to mention these to prescribers.

Keywords Adverse drug reaction; adverse effect; psychiatric adverse effect

Key points

- Psychiatric adverse drug reactions (ADRs) are relatively common and have been reported with a wide range of common medicines
- Psychiatric ADRs include confusion, agitation, panic attacks and more serious effects such as depression and mood swings, and suicidal ideation and attempts
- Psychiatric ADRs can occur in individuals with no previous psychiatric history as well in those with previous or existing psychiatric illnesses
- Patients newly prescribed medicines that are associated with psychiatric ADRs (e.g. efavirenz, isotretinoin, mefloquine, varenicline, high-dose corticosteroids) should be proactively warned to look out for any changes in sleep or behaviour or thinking, and to seek help from their prescriber if they become concerned

Adverse drug reactions (ADRs)

ADRs are defined as unwanted or harmful reactions experienced after taking a medicine in the intended, prescribed manner, where the medicine is thought to have caused the reaction. Psychiatric ADRs are relatively common and can be caused by a wide range of medicines routinely prescribed in medical and surgical specialties. Patients report reactions such as confusion, agitation, panic, mood swings and suicidal ideation, all of which can be distressing and sometimes frightening. Certain ADRs should be reported via the Yellow Card Scheme (UK) if they are severe or unusual, particularly if they are fatal, life-threatening or medically significant, but also if they occur in children or concern recently licensed medications (i.e. those given the black triangle symbol: ▼). ADRs are generally classified into two groups.

Type A reactions – augmented

These are predictable reactions, which are a result of the medicine's normal pharmacological activity (although they may be unrelated to the intended clinical effect) and are commonly dose-related. Most ADRs are of this type (Table 1).

Type B reactions – bizarre

These are idiosyncratic and unpredictable reactions that could not have been predicted from the known pharmacological activity of the medicine. They include hypersensitivity reactions mediated by immunological factors and true allergic reactions. These are less common than type A reactions and are not normally dose-related (Table 1).

Overview of psychiatric adverse drug reactions

Identifying psychiatric ADRs is complex, as most psychiatric disorders have multifactorial causes. For example, depression is relatively common and is more common in people with chronic medical conditions (see *Unipolar Depressive Disorders*, *Medicine* 2016; **44**(**11**): 654–660). Whereas it is possible to consider that a medicine was a contributing factor in the onset of depressive episodes, it is difficult to confirm that it caused depression. In addition, the pattern of psychiatric ADRs (both causal medicines and symptoms) reported in children may differ from that in adults.[1]

Numerous medicines are associated with psychiatric ADRs, ranging from mild to severe and including suicidal ideation. The incidence, pattern of reactions and dose relationship varies between medicines, and the onset of symptoms can be delayed. Consequently, certain medicines should be used with great caution in patients with a previous psychiatric disorder as this increases their risk of developing psychiatric ADRs. Patients and their carers often find psychiatric ADRs frightening. They should be forewarned of the possibility and encouraged to look out for any such symptoms and report them should they occur.

The following are selected examples and this list is neither complete nor exhaustive. It specifically does not include the psychiatric ADRs caused by psychotropics.

Specific drugs/groups (Table 2)

Antiepileptics[2,3]

All antiepileptics are centrally active, although they have a variety of mechanisms of action. Prevalence rates of psychiatric

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Characteristics of adverse reactions

Type A 'augmented'	Type B 'bizarre'
Predictable	Unpredictable
Usually dose dependent	Rarely dose dependent
High morbidity	Low morbidity
Low mortality	High mortality
Responds to dose reduction	Responds to drug withdrawal

Taken from MHRA website: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/Adversedrugreactions/index.htm (accessed 7 October 2016).

Table 1

disorders are higher in people with epilepsy than in the general population. There is a complex interplay between epilepsy and psychiatric diagnoses and symptoms, psychiatric ADRs from antiepileptics and a predisposition to them (including suicidal ideation and attempts).[3]

The incidence of psychiatric ADRs and the specific symptoms vary between agents; starting and discontinuing gradually can minimize the risk. They are more likely in patients with a pre-existing psychiatric history. Psychotic symptoms have been recognized with many antiepileptics, most notably with topiramate,[3] which causes more psychiatric ADRs than other antiepileptics. Antiepileptics tend to cause affective symptoms more often than psychotic symptoms, and sleep disturbances, particularly somnolence, are common. Antidepressants and antipsychotics used in the management of psychiatric ADRs generally reduce the seizure threshold to varying degrees.

Antiparkinsonian treatments

All antiparkinsonian medications can induce delirium and psychosis as a direct result of their dopaminergic activity. Elderly patients with cognitive impairment are particularly vulnerable to these effects. Psychotic symptoms such as visual hallucinations usually respond to a dose reduction, and non-pharmacological methods should also be considered. If these strategies do not help, consider discontinuing the suspected causal agents. If this is not successful or possible, consider adding an atypical antipsychotic, although starting a dopamine antagonist in this context can compromise control of extrapyramidal symptoms. Clozapine is the only antipsychotic that has clearly been shown to improve psychosis in Parkinson's disease. The dopaminergic agonists have been associated with some impulse control behaviours (such as pathological gambling, hypersexuality and compulsive buying) usually in male patients with a young-onset of illness, and in the early years of treatment.

Antiretrovirals for HIV[4]

Numerous antiretrovirals have varying propensity to induce a range of psychiatric ADRs, which have been extensively reviewed. Efavirenz is one of the most problematic, causing psychiatric ADRs (some of which are severe) in up to half of the patients treated. The protease inhibitors have a number of neurological adverse effects but are not generally associated with psychiatric ADRs.

β-Adrenoceptor blockers[2]

β-Adrenoceptor blockers can cause depression, although this is probably less common than previously thought. They commonly cause fatigue and this may have been misinterpreted as a symptom of depression in some reports. Furthermore, the depressive symptoms reported with β-blockers do not typically fulfil the full criteria for a diagnosis of depression.

Corticosteroids[1]

Corticosteroids can cause numerous and complex psychiatric ADRs. The most common are affective (mania, depression, mood lability, mixed affective states), as well as euphoria and insomnia. Mania is usually seen in patients taking short courses, whereas depression tends to be seen during longer courses (>6 months). Psychosis and delirium have been much less frequently reported. Cognitive impairment can occur following both short and longer courses, and dementia has also been reported. The development of psychiatric ADRs is unrelated to previous experience of psychiatric illnesses, and the dose does not predict the onset, severity, type or duration of the psychiatric ADR. Depression and mania have frequently been reported when decreasing or ceasing corticosteroids.

Interferons

Psychiatric ADRs such as depression, delirium and non-specific psychiatric symptoms have been associated with use of interferon, particularly interferon-α. Initiation of treatment with interferon-α has led to a loss of efficacy of previously effective antidepressants as well as the emergence of suicidal ideation. A history of psychiatric difficulties is not usually considered a reason to withhold interferon treatment, but careful interdisciplinary teamworking is required. Interferon-induced depression responds to antidepressants.

Isotretinoin

Isotretinoin has been associated with depression, suicide attempts, aggression and psychosis. It was the only non-psychotropic associated with depression in the top 10 drugs listed in the US Food and Drug Administration database. Suicide has not been associated with other treatments for acne (i.e. antimicrobials).

Postoperative cognitive dysfunction

Confusion after a major operation is relatively common and usually short-lived. If accompanied by other changes in mental function, it is described as postoperative cognitive dysfunction (POCD); its cause is not fully understood.

At the time of an operation, many factors and influences can converge, making POCD more likely. These include the presence of pre-existing conditions (e.g. dementia), and older age and frailty or physical illness. Immediately after the operation, poor hydration, constipation, poor pain control, disturbed sleep and missing regular medicines can contribute. POCD is also thought to be influenced by the type of anaesthetic, being less common if a regional rather than a general anaesthetic is used, although this may not be true for longer lasting or 'late' POCD. However,

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