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,

Summary of psychiatric adverse reactions (ADRs) with commonly used non-psychotropic medicines

Drug	Psychiatric ADR	Comment
ACEIs		
e.g. Captopril, enalapril[2]	Fatigue, hallucinations, delirium, mood disturbances	
Analgesics		
Opiates	Sedation, dysphoria, confusion, mood changes including euphoria, sleep disturbances, hallucinations, psychosis, delirium, dependence	Psychiatric reactions are relatively common with opiates
$5HT_1$ agonists (sumatriptan)	Fatigue, anxiety, panic attacks	
Antibiotics		
Cephalosporins, penicillins, quinolones (including fluoroquinolones), tetracyclines	Sleep disturbances (insomnia and somnolence, abnormal dreams, nightmares), anxiety, delirium and confusional states, depression and agitation, psychotic symptoms (e.g. hallucinations, suicidal ideation)	All antibiotics can cause delirium. Patients with underlying medical conditions can be at higher risk of developing psychiatric ADRs Of the quinolones, ciprofloxacin causes the most psychiatric ADRs, including mood disturbances, agitation and confusion Onset of psychiatric ADRs can be very fast, e.g. after one dose
Antiepileptics[3]		
Carbamazepine	Depression, agitation, sedation, psychosis, cognitive impairment, delirium	Psychosis has also been reported with oxcarbazepine
Ethosuximide	Mood changes, irritability, sleep disturbances, psychosis, delirium	
Levetiracetam	Irritability, depression, mood disturbances, sedation, insomnia, sleep disturbances, aggression, psychosis	
Perampanel	Aggression, anger, anxiety and confusional states Suicidal ideation and attempts	In up to 20% of patients Effects may be dose-related and tend to occur nearer the onset of treatment
Phenytoin	Agitation, insomnia, delirium, psychosis	Psychosis has also been reported with fosphenytoin
Pregabalin	Sleep disturbances, somnolence and insomnia, abnormal dreams, confusion, mood disturbances (euphoria, depression), irritability, agitation, aggression, panic attacks, psychosis	
Tiagabine	Depression and labile mood, anxiety, insomnia, confusion, nervousness, concentration difficulties, aggression, psychosis	
Topiramate	Psychosis, depression and emotional lability, sleep disturbances, cognitive dysfunction, paraesthesia, behavioural changes	Psychosis is much more common with topiramate (6%) than with other antiepileptics. Paraesthesia and cognitive complaints are the most common central nervous system ADRs; paraesthesia is dose-related
Sodium valproate	Sedation, insomnia and sleep disturbances, hallucinations, depression, delirium	
Vigabatrin	Agitation, lethargy, irritability, depression, sleep disturbances, mood disturbances including mania, psychosis, cognitive impairment	Psychosis is more common with vigabatrin (2—4%) than with other antiepileptics although it can be transient

Table 2 (*continued*)

Drug	Psychiatric ADR	Comment
Zonisamide	Agitation, irritability, confusion, depression, labile affect (mood), anxiety, insomnia, sleep disturbances, psychosis, anger and aggression, suicidal ideation and attempt	
Antimalarials		
Chloroquine, mefloquine	Psychosis including hallucinations, panic attacks, suicidal ideation and attempts Anxiety, depression, restlessness, confusion Abnormal dreams/nightmares are very common with mefloquine	Symptoms begin very early in treatment. Patients should be advised to stop treatment if these develop, and seek medical advice Psychiatric ADRs are more common with mefloquine than chloroquine Reactions can even occur after discontinuation of the drug Mefloquine should not be prescribed for patients with an active or a history of a psychiatric diagnosis
Antiparkinsonian treatments		
Levodopa	Visual hallucinations, depression, hypomania, sleep disturbances, abnormal dreams, cognitive impairment, agitation, psychosis, delirium	
Dopamine agonists	Sedation, psychomotor agitation, anxiety, akathisia, sleep disturbances, psychosis, cognitive impairment, delirium, visual hallucinations	These are associated with more psychiatric adverse effects than levodopa
Amantadine	Decreased concentration, sleep disturbances, visual hallucinations, irritability, anxiety, depression, euphoria, fatigue, psychosis, delirium	
Selegiline (MAO-B inhibitor)	Sleep disturbances, agitation, psychosis	
Entacapone (COMT inhibitor)	Sleep disturbances, hallucinations, delirium	
Antiretrovirals — nucleoside reverse transcriptase inhibitors[4]		
Abacavir[4]	Depression, anxiety, nightmares, labile mood, mania, psychosis	Very few cases reported In all reported cases, the patient rapidly returned to baseline after discontinuing the abacavir
Didanosine[4]	Lethargy, nervousness, anxiety, confusion, sleep disturbance, mood disorders, psychosis, mania	Very rarely
Emtricitabine[4]	Confusion, irritability, insomnia	
Zidovudine[4]	Sleep disturbance, vivid dreams, agitation, mania, depression, psychosis, delirium	Psychiatric ADRs are usually dose-related The onset varies widely, from <24 hours to 7 months
Antiretrovirals — non-nucleoside reverse transcriptase inhibitors[4]		
Efavirenz[4]	Agitation, depersonalization, hallucinations, disturbed sleep, vivid dreams, mood disorders including depression, suicidality, hostility, antisocial behaviour, nervousness, irritability, psychosis, catatonia, delirium, cognitive disturbances	Efavirenz can cause psychiatric ADRs in over half of patients treated. Onset is often in the first 2–4 weeks. Symptoms are often intolerable, and some patients choose to stop treatment prematurely. For others, symptoms may resolve in 6–8 weeks without dose adjustment. Severe depression or acute psychosis may necessitate discontinuation. Patients should be advised to seek immediate medical attention if they develop severe

(*continued on next page*)

Table 2 (*continued*)

Drug	Psychiatric ADR	Comment
		depressive symptoms, suicidal ideation or psychotic symptoms A history of psychiatric illness increases the risk of efavirenz-induced psychiatric ADRs
Etravirine[4]	Sleep disturbance	Significantly less frequent than with efavirenz
Nevirapine[4]	Visual hallucinations, persecutory delusions, mood changes, nightmares and vivid dreams, depression	A small handful of cases have been reported Onset of symptoms was within the first couple of weeks Symptoms all resolved on discontinuation of nevirapine
Rilpivirine[4]	Insomnia (very common), abnormal dreams and disturbed sleep, depression	A similar adverse effect profile to efavirenz but a lower incidence of each event
Antiretrovirals — integrase inhibitors[4]		
Elvitegravir[4]	Depression, insomnia; suicidal ideation and attempts in patients with pre-existing psychiatric illnesses	In Phase II trials, 17% of patients developed psychiatric ADRs at 48 weeks (lower incidence than with efavirenz, at 43%)
Raltegravir	Depression, abnormal dreams and nightmares, suicidal ideation, psychosis	In Phase III trials, depressions occurred in up to 2.5% patients
Cardiovascular agents		
β-Adrenoceptor blockers (atenolol, propranolol, sotalol)	Fatigue, sedation, sleep disturbances and nightmares, cognitive impairment, depression, hallucinations, psychosis, delirium	Disturbances are more common with lipid soluble β-blockers (e.g. propranolol)[2] Propranolol is the β-blocker most clearly associated with depressive symptoms, but causality has not clearly been identified even with this drug, only an association through the use of proxy indicators[2] Reports of psychiatric ADRs from numerous clinical trials are mixed
Calcium channel blockers (e.g. diltiazem, amlodipine)	Mood changes, lethargy, dysphoria, mania, psychosis, delirium, akathisia	Causal association is not clearly demonstrated
Statins (simvastatin, atorvastatin, fluvastatin, pravastatin)	Depression, suicidal tendency, emotional lability, aggression, agitation, irritability, anxiety, panic, euphoria, cognitive disorder, sleep disorders, hallucinations, paranoia	Statins penetrate the blood—brain barrier; simvastatin has the highest permeability
Corticosteroids[1,2]		
Glucocorticoids (e.g. betamethasone, prednisolone, prednisone)	Mood disorders, suicidal ideation, euphoria, agitation, sleep disturbances, psychosis and delirium, dementia, cognitive impairment	Causal association is clear with corticosteroids in both adults and children. Symptoms are often serious (warranting psychiatric assistance or admission) The onset of psychiatric ADRs are often very sudden and within the first 1—2 weeks of starting treatment. There is a clear association with increasing dose; symptoms generally respond to a decrease in dose, and have been reported in association with several routes of administration (including oral, parenteral and inhaled), although are probably less common with inhalation Symptoms usually resolve on gradual discontinuation of the corticosteroid, although duration of symptoms varies considerably
Other agents		
Interferons — α and β	Depression, loss of efficacy of previously effective antidepressants, suicidal ideation,	Psychiatric ADRs are relatively unlikely with interferon-β but much more widely reported

Table 2 (*continued*)

Drug	Psychiatric ADR	Comment
	delirium, non-specific psychiatric symptoms Rare case reports of psychosis and mania with interferon-α	with interferon-α Interferon-α-associated depression responds to antidepressants, use of which can be preventive Co-administration of efavirenz (see above) does not further increase the risk of depression[4] Novel diagnostic biomarkers have been investigated to predict which patients are likely to develop interferon-α-associated psychiatric ADRs
Isotretinoin	Depression, suicide, psychosis	Increased risk of suicide continues for up to 6 months after discontinuing treatment. The risk is no higher in those with suicide attempts before initiating isotretinoin. The effect is not related to dose or duration of treatment. If psychiatric changes occur, the drug should be discontinued and psychiatric advice sought
Naltrexone	Dysphoria, fatigue, sleep disturbances, suicidal ideation, hallucinations, delirium	
Postoperative cognitive dysfunction	Confusion, agitation, anxiety, poor concentration, memory loss, sleep disturbances, psychotic symptoms	Onset is usually straight after surgery, usually resolving within a few days. Most common in the elderly
Varenicline[5]	Disturbed dreams and insomnia are very common. Changes in behaviour, anxiety, agitation, aggression, hostility, restlessness, acute psychosis, mood swings, depressed mood or worsening of depression, suicidal ideation and behaviour, attempted suicide Worsening of pre-existing psychiatric disorders	Patients with a psychiatric history are at a greater risk of developing psychiatric ADRs, but suicidal ideation and behaviours have also been reported in patients with without a pre-existing psychiatric disorder Often, but not always, symptoms resolve of discontinuation of varenicline

ACEI, angiotensin-converting enzyme inhibitor; COMT, catechol-O-methyltransferase; MAO, monoamine oxidase.

Table 2

during an operation and postoperatively, numerous medicines are usually administered, including some that have been associated with psychiatric adverse events (e.g. fentanyl, propofol).

Varenicline[5]

A wide range of psychiatric symptoms, some very severe, have been reported through post-licensing monitoring in patients using varenicline to help them stop smoking. Reports have been from both patients with pre-existing mental health illnesses and those without. It is not clear yet how much these new or worsened psychiatric symptoms are related to nicotine withdrawal, and how much to varenicline. A more recent meta-analysis showed no difference in rates of psychiatric ADRs in patients on varenicline compared with placebo. However, if an individual patient develops agitation, depressed mood or changes in mood or suicidal ideation or behaviour, varenicline should be stopped. ◆

KEY REFERENCES

1 Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. *Mayo Clin Proc* 2014; **89:** 817–34.
2 Patten SB. Drug-induced depression: a systematic review to inform clinical practice. *Psychother Psychosom* 2004; **73:** 207–15.
3 Piedad J, Rickards J, Besag FMC, Cavanna AE. Beneficial and adverse psychotropics effects of antiepileptic drugs in patients with epilepsy. *CNS Drugs* 2012; **26:** 319–55.
4 Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. *CNS Drugs* 2014; **28:** 131–45.
5 Gibbons RD, Mann JJ. Varenicline, smoking cessation and neuropsychiatric adverse events. *Am J Psychiatry* 2013; **170:** 1460–7.

FURTHER READING

For details about individual medication prescribers should always refer to the relevant Summary of Product Characteristics available

via the Electronic Medicines Compendium (eMC): www.medicines.org.uk

Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011; **15:** 1–234.

Bazire S. Drug-induced psychiatric disorders. Psychotropic drug directory: the professionals' pocket handbook and aide memoire. Lloyd-Reinhold Communications, 2016. Chapter 5.

Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. *Br Med J* 1998; **316:** 1295–8.

Turjanski N, Lloyd GG. Psychiatric side-effects of medications: recent developments. *Adv Psychiatr Treat* 2005; **11:** 58–70.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 45-year-old woman consulted her GP seeking help with smoking cessation. She had previously tried various nicotine replacement systems and bupropion, but without success. She had recurrent wheezy breathlessness and had depression for which she took fluoxetine. She was overweight, BMI = 30. Varenicline is considered.

What is the most important advice to give her about this treatment?

A Report any worsening of her depression
B Report any changes in weight
C Take adequate contraception measures
D Avoid over-the-counter analgesics
E Avoid alcohol (as it has an Antabuse-like effect)

Question 2

A 35-year-man consulted his GP at the request of his wife, who said that for the previous 10 days he had been acting oddly. He had been very moody, shutting himself away in his office or study, had not been out of the house much except for going to work, and seemed suspicious and uncharacteristically non-communicative. This had all started shortly after he had started antimalarial prophylaxis before a business trip to Africa.

Which antimalarial is most likely to be responsible?

A Chloroquine
B Mefloquine
C Atovaquone
D Proguanil
E Doxycycline

Question 3

A 45-year-old man consulted his GP with low mood and loss of interest in going out, seeing his friends and taking part in other activities that he used to enjoy. His sleep and appetite were also disturbed. He had chronic hepatitis C infection and had been prescribed interferon-α and ribavirin a month previously.

What is the most appropriate action?

A Stop the interferon-α
B Stop the ribavirin
C Discuss prescribing a selective serotonin reuptake inhibitor antidepressant
D Review in a month, with no other treatment
E Refer for cognitive behavioural therapy

