Psychiatric side effects of non-psychiatric drugs

Psychiatric side effects of non-psychiatric drugs are poorly studied. This article describes how to identify and manage the psychiatric side effects of some commonly prescribed medicines that are known to cause such problems.

Psychiatric side effects of drugs used to treat a variety of medical conditions may occur at normal therapeutic and toxic doses. The effects may resemble symptoms seen in other mental disorders. Psychiatric side effects encompass the whole range of psychiatric symptoms from depression or frank psychotic symptoms, to gambling and suicide. This article focuses on psychiatric side effects of the following medicines: interferons, corticosteroids, antiparkinsonian medicines and antimalarials. It describes how psychiatric side effects from these medicines might present and how they might be managed or avoided.

An adverse drug reaction is a harmful and unintended reaction that occurs after administration of a medicine at a dose normally used for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function (Medicines and Healthcare products Regulatory Agency, 2010). Adverse drug reactions have a significant impact on the NHS. In 2002, over 6% of people admitted to hospital had experienced an adverse drug reaction just before admission and adverse drug reactions are estimated to have an annual cost to the NHS of £466 million (Pirmohamed et al, 2004).

Psychiatric side effects of drugs are often poorly studied in clinical trials because they are rare events in standard clinical practice that are grouped together by research instruments as 'psychiatric effects'. The majority of psychiatric side effects of drugs only become apparent after the medicines have been licensed, via post-marketing surveillance.

Diagnosis of a psychiatric side effect can be difficult because of confounding factors in the treatment of an illness. It is important to consider the following factors when attempting to determine if a psychiatric side effect is associated with a medication:

1. The chronology of onset of the suspected psychiatric side effect is important, as this may highlight another substance or factor involved
2. The change in the presentation of a psychiatric side effect on withdrawal and, if possible, re-challenge (stopping and starting the agent in question)
3. Consideration of the individual's underlying psychiatric condition or co-prescribed medicine(s).

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Interferons

Interferons are an effective adjuvant therapy for a variety of melanomas and the treatment of hepatitis C and B virus infection. Interferon-β is licensed for the treatment of multiple sclerosis.

Psychiatric side effects

Interferons have been associated with a wide range of psychiatric side effects, including depressive disorders, insomnia, fatigue, mania (severe agitation and irritability), psychosis, suicidal ideation, cognitive dysfunction, fatigue, sleep disturbances and anorexia.

Of the psychiatric side effects associated with interferon, affective disorders have attracted the most attention. Depressive disorders have been reported in 16–58% of individuals and may appear weeks or months into treatment (Koskinas et al, 2002; Diepernik et al, 2003). Conversely, there are case reports of interferon-α-induced manic states, characterized by severe agitation and irritability (Onyike et al, 2004).

Depressive disorders may be more of a concern with interferon-α than interferon-β. Most studies have ruled out an association between interferon-β and depression or suicide in patients with multiple sclerosis (Kremenchutzky et al 2007). However, there are case reports of depression and suicide resulting from use of interferon-β. There are two forms of interferon-α, of which interferon-α2a may be associated with a lower propensity to cause depression than interferon-α2b (Malek-Ahmadi and Hilsabek, 2007). Patients who have a history of depression should be prescribed interferon-α2a to lower the possibility of worsening or precipitating depression. All patients should receive the more effective treatment for hepatitis C virus of ribavirin and interferon – current evidence suggests that the combination of these medicines does not increase the risk of depression.

Management of interferon's psychiatric side effects

Interferon-induced psychiatric side effects tend to be mild in the majority of individuals and on discontinuation symptoms resolve within 2–3 weeks. Discontinuation of interferon may not always be possible as the individual must complete the course to treat the hepatitis C. In cases where psychiatric side effects are mild, individuals should be monitored every 2 weeks initially to ensure symptoms do not worsen.

Longer durations of interferon therapy are associated with a higher incidence of psychiatric side effects and so the shortest possible course of therapy reduces the risk of psychiatric side effects (Hosoda et al, 2000).

It is likely that the psychiatric side-effect profiles of the two interferon formulations available (pegylated and non-pegylated) are very similar (Raison et al, 2005). It is unlikely that switching between the pegylated and non-pegylated formulation would result in fewer or less severe psychiatric side effects.

Individuals should be screened for depressive disorders before starting interferon treatment and monitored throughout. Having a history of depression or anxiety does not contraindicate interferon therapy, unless the individual is actively suicidal with plans. Interferons do not increase the incidence of development of depression or the rate of treatment discontinuation in individuals with a history of this condition. Suicide attempt and completed suicide have been reported with interferon-α and β. A meta-analysis has indicated that 7% of patients with chronic hepatitis C taking interferon-α suffer depressive symptoms during the first 6 months of treatment (Malek-Ahmadi and Hilsabek, 2007).

Selective serotonin-reuptake inbhibitors are effective for the treatment of interferon-induced depression. Over 80% of interferon-treated patients who develop depression improve when prescribed a selective serotonin-reuptake inbhibitor and a similar proportion of individuals are able to complete treatment (Raison et al, 2005). Prophylactic antidepressant medication should not be offered routinely to all individuals who are found to have a history of depression during pre-treatment screening, as prescribing a selective serotonin-reuptake inbhibitor in this situation may cause a small increase in the risk of haemorrhage, it is unlicensed, and there is a lack of controlled trial data supporting this (Weinrieb et al, 2003). If individuals treated for hepatitis C virus are prescribed a selective serotonin-reuptake inbhibitor, they should be warned about the possible risks of haemorrhage, and told to seek medical advice should they experience any of the following: unexplained bruising, frequent nose bleeds, dark stools, bleeding that fails to clot, blood in bodily secretions or unusually heavy menstruation.

Manic symptoms are associated with interferon dose reductions, pauses in interferon therapy or when interferon-induced depression has been treated with antidepressants. A manic state is a psychiatric emergency which requires action to assess the patient and initiate treatment to control the symptoms. If the individual is taking an antidepressant, it should be stopped immediately. Lithium, valproate or olanzapine have all been used in published cases to treat interferon-induced mania. All these treatments induced a remission in the individual's symptoms (Raison et al, 2005). Benzodiazepines may also aid recovery of mania by at least partly inducing longer periods of sleep in those with insomnia.

Interferon-related fatigue and insomnia may be relieved by good sleep hygiene and other non-pharmacological approaches: improved nutrition, altering periods of rest and activity, increasing aerobic activity, scheduling more strenuous activities during times of peak energy, and ensuring adequate hydration.

Corticosteroids

Corticosteroids have been associated with both affective (depressive, manic or mixed features) and psychotic disorders (delusions or hallucinations, impaired reality and delirium). There have also been reports of euphoria, dysphoria, catatonia, panic attacks and reversible dementia.

Corticosteroid-induced psychiatric side effects are dose related in frequency and severity. Doses of prednisolone of 41–80 mg/day are associated with an incidence of psychiatric side effects of 4.9%, rising to 18.4% with doses above 80 mg/day. However, there are also case reports of psychiatric side effects with low systemic exposure from inhaled corticosteroids (Turktas et al, 1997). Moreover, corticosteroid-treated individuals are three times more likely to develop severe depressive symptoms during an inpatient admission than other individuals (Patten et al, 1996). If present, depressive symptoms usually occur within 5 days of starting a corticosteroid.

Manic symptoms may occur while an individual is receiving corticosteroid treatment and depressive symptoms may develop when an individual stops treatment or the dose of corticosteroid is reduced (Patten and Neutel, 2000).

Adverse effect data from clinical trials have produced little evidence of 'steroid-induced psychosis', and cases of steroid-induced psychosis have been poorly described in published reports. The scenarios in case reports of steroid-induced psychosis might indicate a delirium rather than psychosis (Patten and Neutel, 2000).

Management of psychiatric side effects of corticosteroids

There is a paucity of evidence to identify individuals who have an increased risk of developing psychiatric side effects from corticosteroids. Having a history of mental illness or a single episode of steroid-induced disturbance should not contraindicate the use of corticosteroids (Vincent, 1995). However, if individuals experience a psychiatric side effect from corticosteroids there is an increased risk of recurrence on re-challenge (Goggans et al, 1983).

Should an individual experience a steroid-induced psychiatric side effect, altering the dosing schedule may help alleviate the effects. Splitting oral doses will reduce the peak plasma levels, which is thought to help reduce the severity of symptoms. Pulse treatments (i.e. high dose one day, no drug the next) have also been used to reduce psychiatric side effects.

Mania should be considered a psychiatric emergency and a quick response is required. There are published case reports of successful treatment of corticosteroid-induced mania with numerous antipsychotics (chlorpromazine, haloperidol, olanzapine and risperidone) (Budur and Pozuelo, 2003). Most reports published are of the successful use of olanzapine with doses used ranging from 2.5–15 mg daily, symptoms improved rapidly on starting the antipsychotic, and some patients were able to continue with their steroid treatment. The duration of treatment with olanzapine ranged from 2 weeks to over 3 months, a shorter duration was required if the steroid was reduced or stopped.

Antimalarial chemoprophylaxis

Antimalarial psychiatric side effects have attracted media sensationalism and controversy in the past 15 years. Initial reports of antimalarial psychiatric side effects were reported in army personnel who were used to evaluate new antimalarial chemoprophylaxis treatments. There were very few randomized controlled trials examining antimalarial psychiatric side effects until the early 2000s. It has therefore been difficult to give travellers specific advice on the risk of experiencing psychiatric side effects when deciding to take malaria chemoprophylaxis.

Psychiatric side effects

The most common psychiatric side effects associated with chloroquine are anxiety, depression, sleep disturbances and vivid dreams. The prevalence of psychiatric side effects associated with chloroquine is less than with other antimalarial medicines, with an incidence of between 1 and 5% in individuals taking the medicine. The risk of mania and psychosis with chloroquine use is low, with an incidence of 0.007% (Robert et al, 2004). Psychiatric side effects from antimalarials start after the first dose and are probably dose related (Boudreau et al, 1993). As psychiatric effects start early on initiation of treatment, antimalarials may not have an increased risk of psychiatric side effects on long-term use. However, antimalarials have a raft of other side effects which may become problematic on long-term use of the medicines, such as retinopathy caused by long-term chloroquine use which should be considered if long-term prophylaxis is being considered.

Malarone is a combination of atovaquone and proguanil. The combination is poorly tolerated, with between 22 and 30% of individuals experiencing any type of side effect. Psychiatric side effects reported are mainly strange or vivid dreams in 4–7% and insomnia in 2–3% of individuals (Croft et al, 2002).

A very commonly prescribed antimalarial combination is chloroquine daily and proguanil weekly. These medicines have been have been widely recommended to travellers since the 1980s, and the combination is available to buy from pharmacies. Psychiatric side effects have been reported in 10% of individuals taking the combination (Robert et al, 2004) including: vivid dreams (3%), insomnia (2%), anxiety (<1%) and depression (<1%). Fewer than 0.1% of individuals taking the combination experience psychiatric side effects that interfere with daily activities. It appears that more females than males experience psychiatric side effects (Barrett et al, 1996).

Mefloquine-related psychiatric side effects are seen in over a quarter of all individuals taking the drug. These include strange or vivid dreams (14%), insomnia (13%), anxiety (4%) and depression (4%) (Robert et al, 2004). Nearly 1 in 1000 of individuals taking mefloquine suffer serious psychiatric side effects that require hospitalization; there have been four fatal suicides (Robert et al, 2004). Such serious reports fired media debate as seen on the BBC's 'Watchdog' programme in 1997, and sparked research into antimalarial psychiatric side effects. The first randomized controlled trial comparing mefloquine to Malarone was published in 2001 (Overbosch et al, 2001). The study reported that individuals who received the atovaquone-proguanil combination had fewer treatment-related psychiatric side effects than those taking mefloquine (14% *vs* 29%). There were mainly more sleep disturbances and 'depressive feelings' in those who took mefloquine than those who took the atovaquone-proguanil combination.

Management of antimalarial psychiatric side effects

Psychiatric side effects from antimalarials can emerge within hours of taking the first dose. Most psychiatric side effects tend to be mild or moderate and resolve completely on stopping the drug.

On stopping an antimalarial, improvement in the psychiatric side effect may be delayed because of the long half-lives of the medicines: mefloquine's half life is 7–21 days, chloroquine 1–2 months, proguanil 14–20 hours and atovaquone 2–3 days. It could take over 3 months for mefloquine to be completely eliminated, which could significantly affect the time it takes the individual to improve from the psychiatric side effect.

Severe reactions may require hospitalization and treatment with psychotropic medication. A benzodiazepine or hypnotic may be sufficient to treat some of the milder psychiatric side effects, although more aggressive treatment may be required when the reaction causes psychosis or depression. Selective serotonin-reuptake inbhibitors and/or psychotherapy have been used to treat depression, panic attacks and anxiety related to antimalarials (Beny et al, 2001). Antipsychotics have also been used for extended periods to treat symptoms of psychosis (Beny et al, 2001).

Individuals with a known history of mental illness are at increased risk of developing psychiatric side effects from antimalarials, so prescribing antimalarials in these patients should be avoided where possible. Doxycycline is not associated with psychiatric side effects and it provides effective antimalarial chemoprophylaxis in most areas where there is a variable to high risk of exposure to malaria. Therefore, doxycycline should be prescribed to patients with a history of mental illness.

Antiparkinsonian medicines

Antiparkinsonian medicines are associated with psychiatric side effects such as depression, cognitive impairment, sleep disorders and psychosis. Psychotic symptoms occur in 20–30% of treated individuals. The most common psychiatric side effects are visual hallucinations which usually occur alone (22%) or more rarely with auditory hallucinations (9.7%) (Zahodne and Fernandez, 2008). Hallucinations are vivid, colourful and may involve familiar (possibly deceased) people and or animals. Paranoid delusions are less commonly experienced than hallucinations, dealing with persecution, spousal infidelity or jealousy. In Parkinson's disease the presence of psychotic symptoms in the absence of antiparkinsonian medicines is rare (Bosboom and Wolters, 2004).

While hallucinations and psychosis can be triggered by amantadine and anticholinergics, they are more commonly experienced with dopamine agonists. Dopamine agonists such as pramipexole have greater potential to induce hallucinations than levodopa (21% *vs* 6% respectively) (Bosboom and Wolters, 2004).

Management of psychiatric side effects of antiparkinsonian medicines

Common precipitating factors for delirium and psychosis in Parkinson's disease should be excluded, for example, altered endocrine and metabolic markers, urinary or pulmonary infection or encephalopathy. The general management of psychiatric side effects is through dose reduction and attempted withdrawal of the causative medication. As the psychiatric side effect may occur at any time, it may be difficult to identify the causative medicine.

The first-line treatment of an antiparkinsonian-induced psychiatric side effect should be discontinuation of the Parkinson's disease drugs, one by one. This may alleviate the psychiatric side effect, but it often worsens the individual's motor function. Antiparkinsonian medicines should be gradually removed in the following order: anticholinergics, amantadine, monoamine oxidase B inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitors and then levodopa (Zahodne and Fernandez, 2008). Short-acting formulations of levodopa rather than extended release preparations may also be useful to avoid accumulation.

Where withdrawal and reduction of antiparkinsonian medicines is not successful because of worsening motor function, antipsychotic treatment may be more appropriate.

Olanzapine and clozapine are effective in treating psychotic symptoms in Parkinson's disease (Zahodne and Fernandez, 2008). Clozapine is cumbersome to prescribe because of the mandatory blood monitoring requirements and is associated with problematic side effects such as hypotension, sialorrhoea and sedation. Individuals should be started on very low doses of clozapine (6.25 mg or 12.5 mg), and titrated slowly to a dose of approximately 50 mg/day. Olanzapine has been associated with worsening motor function in 40% of individuals with Parkinson's disease even at low doses and is best avoided. Risperidone is not recommended for antiparkinsonian psychiatric side effects as there is a dose-dependent increase in extrapyramidal side effects, even though clinical data support its efficacy in this instance. Ziprasidone should be avoided as data supporting its effectiveness in treating antiparkinsonian psychiatric side effects are lacking and tolerability is poor. Aripiprazole may be an option: a small study has shown that doses of 0.625 mg/day may be tolerated and improve levodopa-induced dyskinesias in Parkinson's disease patients (Meco et al, 2009). Quetiapine is marginally less effective than clozapine for improving psychotic symptoms in Parkinson's disease (Zahodne and Fernandez, 2008).

The antipsychotic of choice in psychosis associated with Parkinson's disease is quetiapine because of its relatively good tolerability and the ease of its use relative to the other atypical antipsychotics. Again, doses should be started low and increased slowly to avoid adverse motor effects and over-sedation. There are case reports of successful use of antidepressants (i.e. citalopram and clomipramine) in treating psychotic symptoms in Parkinson's disease where there is concomitant depression (Zahodne and Fernandez, 2008).

Given that nearly a quarter of Parkinson's disease patients have dementia, an important consideration is that antipsychotics are thought to increase the risk of mortality two fold and the risk of a cerebrovascular event three fold in elderly individuals with dementia (Anonymous, 2007). Several open label studies have shown that cholinesterase inhibitors may be a useful alternative to antipsychotics in antiparkinsonian medicine-induced psychosis. Rivastigmine has the best efficacy data of the cholinesterase inhibitors, a large placebo-controlled trial showed patients with psychosis in Parkinson's disease had a significant reduction in hallucinations and a reduction in agitation and/or aggression, with no worsening in motor function (Fernandez et al, 2003).

Conclusions

Taking an accurate history of psychiatric symptoms that may be attributed to a medicine and working out the chronology of the symptoms is key to ensuring the accurate diagnosis of a psychiatric side effect. Clinicians should refer to the psychiatric team to develop an appropriate management plan for psychiatric side effects. All

psychiatric severe symptoms should be reported to the Medicines and Healthcare products Regulatory Authority via the yellow card system to ensure that the data on drug-induced psychiatric side effects are improved. **BJHM**

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KEY POINTS

- Diagnose a psychiatric side effect by confirming the chronology of the appearance of the psychiatric symptom and prescribing of the offending agent, taking into consideration other co-morbidities and medicines.
- Refer to psychiatric services for appropriate advice.
- Report all suspected side effects to via the yellow card system.

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