

Advances in neuropsychiatry: clinical implications

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Abstract In this review of recent advances in the sub-specialty, we briefly discuss the current understanding of causes, presentations and evidence-based treatment of the most common disorders seen in clinical neuropsychiatry. Traumatic and acquired brain injury, epilepsy, multiple sclerosis, Parkinson's and Huntington's disease, sleep disorders and delirium are all considered, focusing on the most contentious issues and practical approaches to management and treatment.

The disciplines of psychiatry and neurology have shared a chequered past. At times united, then divided, their current realignment in neuropsychiatry seeks to combine not only the neurological and psychiatric perspectives of brain disorders but also each sub-specialty's skills in their assessment and management. In this review, we discuss how recent advances have informed the neuropsychiatric management of various neurological illnesses. (We have not considered the dementia syndromes or presenile dementias.) Good-quality evidence regarding therapeutic approaches, whether biological or psychological, is often lacking. However, where possible we have highlighted appropriate therapies and treatment strategies.

FOCAL NEUROLOGICAL DISORDERS

Stroke and traumatic brain injury

Both stroke and traumatic brain injury are characterised by acute, usually focal, brain injuries that result in neurological disability, with a subsequent recovery period. The neuropsychiatric presentations associated with these injuries are similar and therefore considered together. Following both stroke and traumatic brain injury, neurological symptoms (such as hemiparesis or dysphasia) are the main cause of disability, but neuropsychiatric symptoms are likely to have a greater negative impact on disability and, possibly, mortality.

Prevalence of neuropsychiatric disorders

Table 1 illustrates the range and prevalence of neuropsychiatric sequelae observed after stroke. Very similar problems, by and large with similar prevalence rates, are observed after traumatic brain injury. However, traumatic brain injury is associated with higher rates of bipolar affective disorder, and particularly of rapid-cycling bipolar disorder with a periodicity of days rather than weeks.

Clinical presentations

Mood disorders

Mood disorders are common in both stroke and traumatic brain injury. They are generally similar to the disorders experienced by people without brain injury, although there is often more evidence of lability of mood and apathy.

Stroke must be regarded as a significant risk factor for suicide (Stenager *et al*, 1998). After traumatic brain injury, the standardised mortality rate from suicide is increased threefold, so that about 1% will die by suicide over a 15-year follow-up, with the risk remaining fairly constant over this period (Teasdale & Engberg, 2001). A study of suicidality after traumatic brain injury found that 35% of individuals had clinically significant levels of hopelessness, 23% had suicidal ideation and 17% had attempted suicide during the 5 years since their injury (Simpson & Tate, 2005).

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Table 1 Psychiatric syndromes associated with stroke

Syndrome	Mean prevalence, % ¹	Clinical features
Depression	35	Feeling miserable or hopeless, tearfulness, demotivation, decreased appetite and weight loss, reduced interactions
Mania	Rare	Elevated mood, decreased sleep, thought disorder, grandiosity
Bipolar affective disorder	Rare	Alternating symptoms of depression and mania
Anxiety disorder	25	Uncontrollable fear or apprehension, restlessness, somatic anxiety symptoms
Apathy without depression	20	Avolition, anhedonia and demotivation
Psychosis	Rare	Delusions and hallucinations
Emotionalism	20	Impairment in the control of crying and, more rarely, laughing
Catastrophic reaction	20	Bursts of aggressive behaviour, anxiety, crying
Cognitive impairment	25	Visuospatial neglect, apraxia, impaired learning, reduced attention

1. Values calculated from prevalence studies. After Chemerinski & Robinson (2000).

Psychosis

Psychosis is a rare but serious complication after traumatic brain injury, presenting both early and late in recovery. When early, it is more likely to be associated with delirium. Head injury has long been thought a possible risk factor for schizophrenia, although a comprehensive critical review of psychosis following head injury concludes that the injury is unlikely to be causal in the disorder (David & Prince, 2005).

Progressive cognitive decline

Brain injury may also be followed by progressive cognitive decline. Dementia pugilistica may develop years after repeated blows to the head, usually in boxers. Head injuries, particularly in men, may predispose to the development of Alzheimer's disease (Fleminger *et al*, 2003b). This is presumably due to deposition of β -amyloid in the brain at the time of injury, although evidence that it is linked to APOE status is inconsistent.

Other neuropsychiatric presentations

Agitation and aggression are relatively infrequent after stroke but are often seen after traumatic brain injury. This partly reflects the individual's personality. Agitation is common in association with the post-traumatic confusional state (see Delirium below). Early agitation predicts long-term, typically explosive aggressive behaviour.

Thoughtlessness, impulsiveness and irritability are particularly troublesome changes in personality

after traumatic brain injury, and a common cause of distress for family and carers. Apathy and poor motivation often compound the problems. Personality change is frequently associated with dysexecutive syndrome, which is manifested in impaired problem-solving owing to difficulties in planning, prioritising and monitoring tasks, and in multi-tasking. Impairments of concentration and memory and psychomotor slowing are also common cognitive symptoms.

Associated conditions

In post-concussion syndrome it can be difficult to disentangle the relative contributions of brain injury and psychological responses. Symptoms include double and blurred vision, noise sensitivity, dizziness, difficulties concentrating, fatigue and head and neck pains. Anxiety and depression tend to occur later. Similar non-specific symptoms are seen in somatisation disorders, including chronic fatigue syndrome. Involvement in a compensation claim may increase post-concussion symptoms, particularly after mild injury such as whiplash.

The psychological symptoms after whiplash are similar to those of post-concussion syndrome. A protracted course, beyond 6 months, is described as late whiplash syndrome. A controlled study of psychological outcomes and predictors following whiplash, compared with other road accident injury, showed no injury-specific psychiatric factors between groups (Mayou & Bryant, 2002). Of particular note was the association between claiming compensation at 3 months and pain at 1 year.

Aetiology

There has been a long-standing debate as to whether there is an association between the location of the brain lesion (particularly anterior, left-hemisphere lesions) and post-stroke depression. A systematic review suggested that there is no evidence to support such a relationship (Carson *et al*, 2000). However, the methodology of this review, particularly the exclusion of some studies, has been criticised. A subsequent meta-analysis re-ignited the debate and suggested that proximity of the lesion to the left frontal pole predicts depressive illness (Narushima *et al*, 2003). This was further supported by another appraisal from Finland (Vataja *et al*, 2004).

Most traumatic brain injury is caused by closed head injury and is often complicated by alcohol. The vulnerability to contusions of areas of the brain that are involved in social behaviour, cognition and regulation of mood (medial orbitofrontal and anterior temporal lobes) (Tranel *et al*, 2000) partly explains why the neuropsychiatric consequences of traumatic brain injury usually outstrip the neurological sequelae as predictors of outcome. The best predictor of outcome is the duration of post-traumatic amnesia, the period from injury to the return of continuous day-to-day memory. People with post-traumatic amnesia that lasts longer than 1 month are unlikely to return to work.

Treatment

It is important to be vigilant in identifying post-stroke depression, and treatment of depressive symptoms should always be considered (Box 1). The fact that they are 'understandable' or are symptoms that may be a direct consequence of brain injury (e.g. apathy) should not prevent a trial of an antidepressant. It has been suggested, on the basis of limited evidence, that the D₂-receptor agonist bromocriptine might have therapeutic benefit in the management of apathy.

There is very limited evidence from systematic reviews regarding the efficacy of antidepressants in treating post-stroke depression (Turner-Stokes & Hassan, 2002). Although there is the suggestion that tricyclic antidepressant drugs are more effective, selective serotonin reuptake inhibitors (SSRIs), having fewer side-effects, are a reasonable first choice (Box 2).

There is increasing interest in the early prescription of antidepressants after stroke as a preventive strategy for mood disorder. However, a review of treatment trials found no prophylactic effect of antidepressants compared with placebo (Anderson *et al*, 2004). It has been suggested that treatment of

Box 1 National clinical guidelines for the management of mood disturbance after stroke

- Provide information, advice and the opportunity to talk about the impact of the stroke
- Assess psychosocial needs
- Screen for depression and anxiety within the first month of stroke and monitor mood
- With those who can respond use standardised questionnaires for screening
- Confirm emotionalism by a few simple questions at interview
- If one mood disorder is present assess for the others
- Severe, persistent or troublesome tearfulness (emotionalism) should be treated with antidepressants; the frequency of crying should be monitored to check effectiveness
- Consider a trial of antidepressant medication in those with persistently depressed mood of at least 1 month's duration
- If there is a good response, antidepressants should be continued for at least 6 months

After Intercollegiate Working Party for Stroke (2004: pp. 53–54).

Box 2 Factors influencing choice of psychotropic medications

- Side-effects of the medication, particularly on cognitive function as a result of anticholinergic effects
- Whether the drug is generally sedative, useful in agitation or anxiety, or alerting
- Drug interactions, particularly with anticoagulant, cardiac and antiparkinsonian medications
- Drug efficacy in the population of interest
- Potential for reducing seizure threshold

post-stroke depression in the first month when compared with the third month benefits functional outcome at up to 2 years (Narushima & Robinson, 2003).

If all else fails, electroconvulsive therapy should be considered. This has been shown to be safe for the treatment of depression after both stroke and traumatic brain injury (Currier *et al*, 1992).

Antidepressants are useful in treating emotionalism (lability of mood, emotional incontinence), regardless of the presence of depression.

Several psychotropic drugs have been used in the management of agitation and/or aggression in

people with acquired brain injury, without clear evidence of their efficacy. A review (Fleminger *et al*, 2003a) reported that beta-blockers have the best evidence supporting their efficacy in treating these behavioural symptoms. None the less, in view of the large doses used in these studies, which were associated with significant side-effects, they should be prescribed with caution and, ideally, with the patient's consent. Carbamazepine is commonly used as a first-choice medication in this setting, despite the lack of research evidence for its efficacy. Sodium valproate may be used as an alternative. Response to medication is usually seen early, within the first 6 weeks, and it is suggested that this is an adequate period during which clinical benefit should be expected before switching to an alternative treatment. There is no evidence that aggression is different from agitation in terms of its response to medication (Fleminger, 2003).

Olanzapine or quetiapine are reasonable anti-psychotics for psychosis associated with traumatic brain injury, because they have fewer extrapyramidal side-effects.

There is little evidence for psychological interventions for post-stroke depression. Of those used in case studies and series reviewed by Kneebone & Dunmore (2000), cognitive-behavioural therapy (CBT) showed the most promise. However, a small randomised controlled trial reported subsequent to this found CBT to be ineffective (Lincoln & Flannaghan, 2003). Similarly, for other acquired brain injuries, there is only scarce evidence supporting such psychological strategies (Khan-Bourne & Brown, 2003). Early educational interventions after traumatic brain injury may prevent later symptoms.

Multiple sclerosis

Prevalence of neuropsychiatric disorders

The neuropsychiatric presentations of this multifocal demyelinating disorder are varied and include mood, anxiety, cognitive and psychotic disorders. It has been suggested by several studies that the prevalence of depression in multiple sclerosis is higher than in control groups with different neurological illnesses. However, methodological problems have been cited, particularly with regard to clinician masking and diagnostic criteria. A lifetime prevalence for depressive symptoms of 40–50% is generally accepted (Siegert & Abernethy, 2005). Psychotic illness in multiple sclerosis is most commonly observed in the context of treatment with steroids, where it is most often an affective psychosis, although schizophreniform psychoses are also seen.

Cognitive impairment in multiple sclerosis has been estimated to have a prevalence of up to 50% in community samples.

Clinical presentations

Some depressive symptoms are probably more common than others in multiple sclerosis. Of these, fatigue and cognitive impairment have received the most attention. Generally, older studies have suggested that neither of these is correlated with depression in the disorder. However, more recent studies have supported positive correlations, suggesting that mental fatigue (Schreurs *et al*, 2002) and impaired effortful information processing (Arnett *et al*, 1997) in particular are features of the depression. Suicide rates in people with multiple sclerosis have been shown to be twice the mean rate seen in the adjusted population (Stenager *et al*, 1992) and are associated with living alone, alcohol misuse and depressive disorder.

Cognitive deficits arise early in the course of multiple sclerosis and often before the diagnosis has been made. The course of cognitive decline appears to be slow in the majority of cases, although risk factors for a more rapid decline include disease progression, age and worsening of physical disability. Particular impairment is seen in verbal fluency, comprehension, naming and executive dysfunction, as well as memory.

Aetiology

Beta-interferon has been implicated as a cause of depression, although the evidence for this is contentious. Neuroimaging studies of lesion location have been conducted in individuals with multiple sclerosis and depression or psychosis. The most robust findings in depression implicate more hyperintense lesions in left inferior medial frontal regions and greater atrophy of left anterior temporal regions (Feinstein *et al*, 2004). It has been suggested that location of temporal lobe lesion may correlate with psychotic illness (Feinstein *et al*, 1992).

Treatment

Desipramine has been shown to be more effective than placebo for depression in multiple sclerosis, although anticholinergic side-effects may preclude its use. The SSRIs are a good first-line choice although they can cause sexual dysfunction.

Limited evidence exists regarding the best choice of antipsychotic for treatment of psychosis in multiple sclerosis, although an atypical antipsychotic is a sensible choice.

Table 2 Neuropsychiatric associations with epilepsy

<i>Symptoms or syndromes</i>	<i>Frequency and associations</i>
Depression	30-50%. Possible relationship with lesion location, e.g. in temporal lobe epilepsy. Demoralisation and stigma. Increased mortality secondary to suicide
Panic disorder	Lifetime prevalence 21%. Can be inter-ictal and peri-ictal; need for differentiation of panic from seizure activity
Psychosis	Prevalence of between 3 and 7% (from studies that did not use operationalised criteria for schizophrenia or differentiate schizophrenia-like psychoses of epilepsy from episodic psychosis). More common in partial epilepsies. Possible role of mesial temporal and extratemporal damage as risk factor
Episodic	Most commonly post-ictal or drug-induced. Affective, psychotic and confusional phenomena lasting up to a week
Chronic interictal/schizophrenia-like psychoses of epilepsy	Debate as to whether chance association or separate disorder. Inconclusive evidence of increased risk of psychosis in temporal lobe epilepsy or with left-sided focus
Non-epileptic seizures	Abnormal illness behaviour. Generally lack features of epileptic seizures but can be difficult to differentiate. Physical/sexual abuse in childhood

After Schwartz & Marsh (2000).

People with multiple sclerosis treated in an open trial of donepezil showed a reduction in cognitive impairment (Greene *et al*, 2000).

Individuals with fatigue may benefit from approaches used for chronic fatigue syndrome. Cognitive-behavioural therapy for depression is likely to be useful and it has been found to have similar outcomes to treatment with an SSRI (Mohr *et al*, 2001).

Epilepsy and non-epileptic seizures

Prevalence of neuropsychiatric disorders

Neuropsychiatric disorder has been estimated to occur in 6% of people with epilepsy, rising to 10–20% in those with temporal lobe and/or refractory epilepsy. Non-epileptic seizures, which come under the rubric of conversion disorders or dissociative states, are an important differential diagnosis of epilepsy. It has been estimated that between 9 and 50% of patients referred to specialist epilepsy centres have non-epileptic episodes (Francis & Baker, 1999). The most common neuropsychiatric disorders associated with epilepsy and their prevalence are summarised in Table 2.

Clinical presentations

In all presentations in epilepsy, it is important to distinguish between symptoms that are associated with seizures and those that are independent of seizures. Perhaps most importantly, differentiation

of the relationship of neuropsychiatric presentations to the seizure, i.e. whether they are pre-ictal, post-ictal or inter-ictal, is paramount in guiding treatment planning, as this may influence whether the clinician manipulates anti-epileptics, or adds psychiatric medications or does both (see below).

Mood disorders

As with other neuropsychiatric disorders in this setting, depression can be related to pre-ictal events or can be inter-ictal. There has been recent interest in inter-ictal dysphoric disorder, in which people with temporal lobe epilepsy experience at least three symptoms of depressed mood, pain, irritability, decreased energy, sleeplessness, anxiety and intense fear or euphoria (Blumer *et al*, 2004).

Psychoses

Post-ictal psychosis often follows an increase in seizure frequency or a cluster of seizures. It commonly presents with changes in mood, paranoid delusions and hallucinations. These often remit spontaneously within days.

Inter-ictal psychosis resembles schizophrenia, but presents more frequently with visual rather than auditory hallucinations.

Non-epileptic seizures

There is no completely reliable method of discerning dissociative from epileptic seizures. Dissociative seizures can co-exist with epilepsy, and are associated with sexual abuse and female gender. Assessment

should include thorough history-taking (Box 3), an electroencephalogram (EEG) and careful description or, preferably, video recording of pre-ictal, ictal and post-ictal events. Increased post-ictal serum prolactin concentrations (>1000 IU/l) despite normal baseline levels are found after epileptic seizures (Brown & Trimble, 2000), but measurements must be taken within 15 min of the event.

Aetiology

Combinations of biological and psychosocial factors are likely to play a role in the aetiology of neuropsychiatric disorders in epilepsy. In depressive disorders, these factors include anti-epileptic-induced effects such as folate deficiency and frontal lobe dysfunction. In psychoses, hippocampal damage and chronic inhibitory neurophysiological changes may be involved. The hypothesis of forced normalisation, where the abnormal EEG is normalised by anti-epileptic drugs, remains popular. This is based on the observation that the EEG recordings of patients normalised during psychotic episodes and that normalisation induced by anti-epileptics may be an aetiological factor for psychoses. Forced normalisation has been reported in both temporal lobe and generalised epilepsies. A paranoid psychosis has been its most frequent manifestation and it has been observed following the use of various medications, including phenytoin, carbamazepine, ethosuximide and levetiracetam. Forced normalisation may not be restricted to psychoses in epilepsy, but may also present as episodes of major depression.

The social stigma associated with epilepsy is a key psychosocial risk. A critical review of studies of the aetiology of non-epileptic seizures reported that a history of abuse or trauma was identified in between 15 and 40% more people who experienced seizures than in control groups (Fisman *et al*, 2004).

Treatment

It is important to identify the relationship of the psychiatric disturbance to ictal events, the role of anti-epileptic drugs in the aetiology of symptoms and the importance of psychosocial factors. For symptoms related directly to the seizure itself, optimal control of seizures is the treatment of choice.

When considering psychotropic medication for people with epilepsy there is always the concern that the medication will decrease the seizure threshold. However, a retrospective study has suggested that psychotropic medication does not increase mean seizure frequency (Gross *et al*, 2000).

Box 3 Factors in the history that may support a diagnosis of non-epileptic seizures

- Past psychiatric history
- More likely to express distress in a physical way
- History of social stressors
- Seizures more likely to happen in the daytime and when others are present
- Less likely to sustain injury from seizures
- More likely to maintain body tone during a seizure
- Regaining alertness and orientation rapidly
- Ability to recall events clearly

It is important to start psychotropic medication at a low dose and increase it slowly. The SSRIs may be less likely to reduce the seizure threshold than tricyclic antidepressants. Because there may be an interaction between psychotropics and anti-convulsants (for example fluoxetine may increase carbamazepine levels), levels of anticonvulsant should be closely monitored.

It should also be borne in mind that anti-epileptic drugs, often also used routinely to stabilise mood, can be associated with adverse neuropsychiatric reactions. Valproate-induced hyperammonaemic encephalopathy, which presents with impaired consciousness and focal neurological signs, may well go unrecognised if somnolence, decreased motor activity and increased lethargy are misinterpreted as a therapeutic response in patients with mania. Additional symptoms may include subtle personality change, confusion, vomiting and hyperventilation. These clinical features of hyperammonaemia are very variable, can be episodic and are often difficult to detect early. Being aware of a history of similar symptoms and a family history is useful. Serum ammonia levels should be measured and expert advice sought (Hawkes *et al*, 2001).

Haloperidol and sulpiride may be less epileptogenic than other antipsychotics, and therefore the treatment of choice for epileptic psychoses. There is limited clinical experience and few systematic studies of atypical antipsychotics in epilepsy and they should be used with care. Clozapine is particularly epileptogenic and, as always, a balance of risks and benefits must be considered, discussed with the patient and carefully documented when commencing atypical antipsychotic treatment in epilepsy.

Recent work suggests that CBT may be effective in the treatment of non-epileptic seizures (Goldstein *et al*, 2004).

DISORDERS OF THE BASAL GANGLIA

Several neural circuits that link the frontal cortex, thalamus and basal ganglia are involved in movement, attention, memory and reward processes. This may explain why disorders of the basal ganglia are characterised by abnormalities of movement, mental state and cognitive function (Ring & Serra-Mestres, 2002). In this section we briefly discuss Parkinson's and Huntington's diseases.

Parkinson's disease

Prevalence of neuropsychiatric disorders

The common neuropsychiatric presentations and their prevalence rates are outlined in Table 3.

Clinical presentations

Mood disorders

Depression is associated with faster disease progression and more rapid decline in cognitive function and activities of daily living, and is a risk factor for dementia in Parkinson's disease.

Other neuropsychiatric presentations

Psychosis in Parkinson's disease, often with visual hallucinations, persecutory delusions and pathological jealousy, is associated with cognitive impairment and recent increases in antiparkinsonian medication.

The differences between the dementia of Parkinson's disease and Lewy body dementia remain a

topic of debate. Features of Lewy body dementia include fluctuating cognition, visual hallucinations and parkinsonism. The diagnosis cannot be made if parkinsonism developed more than 1 year before the onset of dementia.

In hedonistic homeostatic dysregulation people with Parkinson's disease take increasingly more dopamine-replacement medication, particularly subcutaneous apomorphine, despite dyskinesic adverse effects. They also show hypersexuality, hypomanic symptoms and pathological gambling and shopping while on high doses of dopamine agonists. This uncommon neuropsychiatric syndrome causes significant distress to patients and carers and its recognition is paramount in guiding appropriate management, as it can be commonly mistaken for other neuropsychiatric presentations.

Aetiology

It is probable that both biological and psychological factors explain depression in Parkinson's disease:

- biological – loss of monoaminergic neurons; hypometabolism in caudate, inferior orbito-frontal and medial frontal regions on positron emission tomography
- psychological – chronic disabling illness, psychosocial stress.

As previously stated, psychoses in Parkinson's disease are often related to recent increases in antiparkinsonian medications. History of psychiatric illness, personality disorder or a family history of addiction disorders may predispose patients to hedonistic homeostatic dysregulation.

Table 3 Neuropsychiatric complications of Parkinson's disease

Psychiatric manifestations	Frequency	Associations
All psychiatric symptoms	70%	
Depression	50%	Female; younger onset; prominent right-sided signs, bradykinesia and gait disturbance; depression is possibly correlated with disease progression, poorer cognitive status and activities of daily living
Hypomania/euphoria	2%/10%	Levodopa and dopamine agonist treatment especially in pre-existing bipolar affective disorder
Anxiety	40%	Depression; younger patients
Apathy	Common	Executive impairment
Psychosis	40% (drug-related)	Dopaminergic/anticholinergic medications; hallucinations 20% (especially visual); delusions 3–30%
Cognitive impairment	19% with no dementia	Older patients, late-onset Parkinson's disease; low socio-economic status and education; severe extrapyramidal signs

Treatment

The evidence base for treatment of depression in Parkinson's disease has been examined in a literature review and found to be limited (Ghazi-Noori *et al*, 2004). Tricyclic antidepressants have been shown to be effective in depression in Parkinson's disease and may also improve motor symptoms by virtue of their anticholinergic activity (Rascol *et al*, 2002). However, their side-effects, including cognitive impairment, may limit their use. Although SSRIs generally have fewer side-effects, the evidence that they work is not as strong, and some have extrapyramidal effects that exacerbate motor symptoms.

In psychosis, consideration should be given to decreasing or stopping antiparkinsonian drugs. Antipsychotic medications must be used with caution because of their extrapyramidal side-effects. There is good evidence that low-dose (<100 mg/day) clozapine can improve psychosis without worsening parkinsonism (Parkinson Study Group, 1999). Its use in patients with ischaemic heart disease, particularly elderly people, must be monitored carefully, as it can cause agranulocytosis and tachycardia. There is more limited evidence for the use of other atypicals, cholinesterase inhibitors (Bergman & Lerner, 2002) and odansetron to treat psychotic symptoms.

There is no current evidence supporting the use of cholinesterase inhibitors in dementia in Parkinson's disease, although a randomised placebo-controlled trial has shown benefit with rivastigmine in Lewy body dementia (McKeith *et al*, 2000).

Psychological treatments for depression in Parkinson's disease have not been evaluated fully.

Huntington's disease

Huntington's disease is transmitted by a single autosomal dominant gene on the short arm of chromosome 4. The specific genetic defect has been identified as an expansion of the trinucleotide sequence CAG. In generations who inherit the disorder, the unstable sequence becomes longer, leading to the phenomenon of 'anticipation', whereby later generations manifest the disease at a younger age.

Prevalence of neuropsychiatric disorders

Estimates of the prevalence of psychiatric symptoms at the first presentation of Huntington's disease are in the region of 30%. By and large, the neuropsychiatric presentations and their prevalence mirror those seen in Parkinson's disease. In 3-6% of cases a schizophreniform psychosis is the first presentation of Huntington's disease.

Clinical presentation

There has been significant interest in cognitive abnormalities in gene carriers identified by predictive testing prior to the full manifestation of the disease. The results have, unfortunately, been contradictory. Dispute remains as to whether there are cognitive differences between carriers and non-carriers, as well as to whether cognitive symptoms precede motor symptoms or *vice versa* (Witjes-Ané *et al*, 2003). Since George Huntington's original description of the disorder, it has been well recognised that there is an increased rate of suicide in this group (Schoenfeld *et al*, 1984).

Aetiology

Attempts (albeit with flawed methodologies) have been made to link the psychiatric signs and symptoms of Huntington's disease to the length of the CAG repeat sequence, but no relationship has been found (Weigell-Weber *et al*, 1996).

Treatment

There are no controlled trials establishing the benefit of antidepressants for depression in Huntington's disease. Atypical antipsychotics are preferable for psychoses, so as to avoid exacerbation of motor problems.

OTHER PSYCHIATRIC DISORDERS

Delirium

Clinical presentation

Delirium, often called an acute confusional state, is characterised by a disturbance of conscious level. The patient is obtunded (drowsy) or highly distractible. Attention and concentration are impaired (e.g. as demonstrated by poor performance on a digit span test). Mental state may fluctuate. The individual is neither alert nor oriented, and is likely to be agitated and frightened. Psychotic symptoms with hallucinations, often visual, and fleeting delusions may be elicited. Delirium may also present as a hypoactive withdrawn state akin to stupor.

Aetiology

A diagnosis of delirium always suggests an underlying physical or biological aetiology, and numerous physical problems, including drugs and drug withdrawal, may be aetiological factors.

Agitation is often present in delirium. If the patient has been treated with antipsychotics an important differential diagnosis of the agitation is akathisia. Poor sleep, pain, constipation and systemic illness may play a role.

Treatment

Management consists of making the patient safe and then seeking the underlying biological cause as well as treating the condition symptomatically. Nursing should take place in a well-lit side room with consistent staff. The environment should be calm and allow undisturbed sleep (Inouye *et al*, 1999).

Some patients will settle with reassurance and explanation. Relatives may be able to help. Haloperidol and lorazepam may be used to produce rapid sedation to manage agitation and aggression. The patient should be placed on regular nursing observations, with monitoring of respiration and neurological state. If sedation is required for more than 1 or 2 days, consider atypical antipsychotics such as olanzapine or quetiapine, which are less likely to produce extrapyramidal side-effects. If antipsychotics are not tolerated or cause intolerable side-effects, valproate, carbamazepine and beta-blockers may be helpful alternatives. Avoid drug combinations that may increase agitation and aggression by increasing confusion.

Sleep disorders

In this section, we briefly identify the sleep disorders whose presentations may initially be referred to the psychiatrist.

Narcolepsy

Prevalence

Narcolepsy is uncommon, with a prevalence of 0.025% in the general population.

Clinical presentations

Narcolepsy classically presents as excessive daytime sleepiness, with narcoleptic attacks, cataplexy (where the individual falls owing to sudden loss of muscle tone provoked by strong emotion, seen in 75% of patients), sleep paralysis (inability to move on waking or going to sleep, seen in 30%) and hypnagogic hallucinations (auditory, visual or tactile hallucinations on going to sleep). Only 10% of individuals present with all four phenomena. Alongside this tetrad, automatic behaviours have been reported in around one-third of patients. In

these, despite appearing to be half-asleep, individuals engage in complex behaviours that are not recalled when they regain alertness.

Aetiology

Narcolepsy can be either familial or sporadic and a strong association with HLA haplotypes has been established. The HLA-DQB1*0602 marker is present in almost all individuals with narcolepsy and cataplexy, regardless of ethnicity. Hypocretins (orexins) are hypothalamic neuropeptides believed to play a role in regulating sleep and arousal. Abnormally low concentrations of hypocretin-1 (orexin-A) have been found in the cerebrospinal fluid of patients with narcolepsy. Research has also suggested a deficiency of hypocretin-2 in both narcolepsy and primary hypersomnia (Ebrahim *et al*, 2003).

Diagnosis and treatment

Investigation with overnight polysomnography often reveals sleep latency of less than 10 min and sleep-onset rapid eye movement (REM) periods. The multiple sleep latency test (Carskadon *et al*, 1986), which confirms the presence or absence of REM activity as the patient begins to nap, is also helpful in supporting the diagnosis.

Management is focused on stopping or decreasing narcoleptic or cataplectic attacks. Stimulants such as methylphenidate or the newer modafinil have been shown to be effective.

REM sleep behaviour disorder

Clinical presentation

Individuals with REM sleep behaviour disorder act out their dreams, with limited awareness of their surroundings and often with violent or dangerous consequences that result in physical harm to themselves, property or others. The episodes arise during the middle to latter third of the night during REM sleep and are associated with loss of the normal atonia of REM sleep.

Aetiology

Rapid eye movement sleep behaviour disorder may occur idiopathically or together with disorders such as Parkinson's disease, diffuse Lewy body disease, multiple system atrophy and Gullian-Barré syndrome. It has been reported that it can precede the diagnosis of a movement disorder by several years. As all episodes are associated with a loss of atonia, it is likely that the associated lesions are situated in the brainstem.

Treatment

Treatment with clonazepam has been shown to be effective, although making the sleeping environment safe is a sensible first-line measure.

CONCLUSIONS

The historical division that has existed between neurology and psychiatry is narrowing, much to the benefit of all patients with 'brain disorders'. In this review we have sought to highlight some of the key clinical psychiatric presentations in neurological settings, as well as drawing attention to the associations between neurological illness and psychiatric syndromes. Often, treatment approaches (Box 4) are limited by poor-quality evidence and neuropharmacological complexity. Fortunately in the UK, neuropsychiatry is increasingly being recognised as a clinical subspecialty, closely linked to general liaison psychiatry. If we are to continue to develop treatments for neuropsychiatric disorders and put them into practice then service developments, including closer liaison between neurology and psychiatry, will be necessary.

Declaration of interest

None.

References

- Anderson, C. S., Hackett, M. L. & House, A. O. (2004) Interventions for preventing depression after stroke. *Cochrane Library*, issue 3. Oxford: Update Software.
- Arnett, P. A., Rao, S. M., Grafman, J., et al (1997) Executive functions in multiple sclerosis: an analysis of temporal ordering, semantic encoding, and planning abilities. *Neuropsychology*, **11**, 535–544.
- Bergman, J. & Lerner, V. (2002) Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. *Clinical Neuropharmacology*, **25**, 107–110.
- Blumer, D., Montouris, G. & Davies, K. (2004) The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. *Epilepsy and Behavior*, **5**, 826–840.
- Brown, R. J. & Trimble, M. R. (2000) Dissociative psychopathology, non-epileptic seizures and neurology. *Journal of Neurology, Neurosurgery and Psychiatry*, **69**, 285–288.
- Carskadon, M. A., Dement, W. C., Mitler, M. M., et al (1986) Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. *Sleep*, **9**, 519–524.
- Carson, A. J., MacHale, S., Allen, K., et al (2000) Depression after stroke and lesion location: a systematic review. *Lancet*, **356**, 122–126.
- Chemersinski, E. & Robinson, R. G. (2000) The neuropsychiatry of stroke. *Psychosomatics*, **41**, 5–14.
- Currier, M. G., Murray, G. B. & Welch, C. C. (1992) Electroconvulsive therapy for post stroke depressed geriatric patients. *Journal of Neuropsychiatry and Clinical Neurosciences*, **4**, 140–144.

Box 4 Key points

- Effective practice demands clear communication between the neurologist and psychiatrist
- Always search for physical causes for symptoms, particularly in people with delirium and agitation, and consider effects of drugs, both prescribed and misused
- Start low and go slow when prescribing psychotropics, and avoid drug cocktails
- Do not leave depressive symptoms untreated; SSRIs are generally a safe first choice antidepressant
- When deciding on an antipsychotic for someone with brain injury or with Parkinson's disease choose one with fewer extrapyramidal side-effects
- When prescribing psychotropics in epilepsy monitor anticonvulsant levels

- David, A. S. & Prince, M. (2005) Psychosis following head injury: a critical review. *Journal of Neurology, Neurosurgery and Psychiatry*, **76** (suppl. 1), i53–60.
- Ebrahim, I. O., Sharief, M. K., de Lacy, S., et al (2003) Hypocretin (orexin) deficiency in narcolepsy and primary hypersomnia. *Journal of Neurology, Neurosurgery and Psychiatry*, **74**, 127–130.
- Feinstein, A., du Boulay, G. & Ron, M. A. (1992) Psychotic illness in multiple sclerosis. A clinical and magnetic resonance imaging study. *British Journal of Psychiatry*, **161**, 680–685.
- Feinstein, A., Roy, P., Lobaugh, N., et al (2004) Structural brain abnormalities in multiple sclerosis patients with major depression. *Neurology*, **62**, 586–590.
- Fizman, A., Alves-Leon, S. V., Nunes, R. G., et al (2004) Traumatic events and posttraumatic stress disorder in patients with psychogenic nonepileptic seizures: a critical review. *Epilepsy and Behavior*, **5**, 818–825.
- Fleminger, S. (2003) Managing agitation and aggression after head injury. *BMJ*, **327**, 4–5.
- Fleminger, S., Oliver, D. & Greenwood, R. (2003a) Pharmacological management of agitation or aggression in people with acquired brain injury. *Cochrane Library*, issue 2. Oxford: Update Software.
- Fleminger, S., Oliver, D., Lovestone, S., et al (2003b) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on. A partial replication. *Journal of Neurology, Neurosurgery and Psychiatry*, **74**, 857–862.
- Francis, P. & Baker, G. A. (1999) Non-epileptic attack disorder (NEAD): a comprehensive review. *Seizure*, **8**, 53–61.
- Ghazi-Noori, S., Chung, T. H., Deane, K. H. O., et al (2004) Therapies for depression in Parkinson's disease. *Cochrane Library*, issue 3. Oxford: Update Software.
- Goldstein, L. H., Deale, A. C., Mitchell-O'Malley, S. J., et al (2004) An evaluation of cognitive behavioral therapy as a treatment for dissociative seizures: a pilot study. *Cognitive and Behavioral Neurology*, **17**, 41–49.
- Greene, Y. M., Tariot, P. N., Wishart, H., et al (2000) A 12-week, open trial of donepezil hydrochloride in patients with multiple sclerosis and associated cognitive impairments. *Journal of Clinical Psychopharmacology*, **20**, 350–356.
- Gross, A., Devinsky, O., Westbrook, L. E., et al (2000) Psychotropic medication use in patients with epilepsy: effect on seizure frequency. *Journal of Neuropsychiatry and Clinical Neurosciences*, **12**, 458–464.

- Hawkes, N. D., Thomas, G. A., Jurewicz, A., *et al* (2001) Non-hepatic hyperammonaemia: an important, potentially reversible cause of encephalopathy. *Postgraduate Medical Journal*, **77**, 717–722.
- Inouye, S. K., Bogardus, S. T., Charpentier, P. A., *et al* (1999) A multicomponent intervention to prevent delirium in hospitalised older patients. *New England Journal of Medicine*, **340**, 669–676.
- Intercollegiate Working Party for Stroke (2004) *National Clinical Guidelines for Stroke* (2nd edn). London: Royal College of Physicians. http://www.rcplondon.ac.uk/pubs/books/stroke/stroke_guidelines_2ed.pdf
- Khan-Bourne, N. & Brown, R. G. (2003) Cognitive behaviour therapy for the treatment of depression in individuals with brain injury. *Neuropsychological Rehabilitation*, **13**, 89–107.
- Kneebone, I. I. & Dunmore, E. (2000) Psychological management of post-stroke depression. *British Journal of Clinical Psychology*, **39**, 53–65.
- Lincoln, N. B. & Flannaghan, T. (2003) Cognitive behavioural psychotherapy for depression following stroke: a randomized controlled trial. *Stroke*, **34**, 111–115.
- Mayou, R. & Bryant, B. (2002) Psychiatry of whiplash neck injury. *British Journal of Psychiatry*, **180**, 441–448.
- McKeith, I., Del Ser, T., Spano, P., *et al* (2000) Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*, **356**, 2031–2036.
- Mohr, D. C., Boudewyn, A. C., Goodkin, D. E., *et al* (2001) Comparative outcomes for individual cognitive behaviour therapy, supportive expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *Journal of Consulting and Clinical Psychology*, **69**, 942–949.
- Narushima, K. & Robinson, R. G. (2003) The effect of early versus late antidepressant treatment on physical impairment associated with post-stroke depression: is there a time-related therapeutic window? *Journal of Nervous and Mental Disorders*, **91**, 645–652.
- Narushima, K., Kosier, J. T. & Robinson, R. G. (2003) A reappraisal of poststroke depression, intra- and inter-hemispheric lesion location using meta-analysis. *Journal of Neuropsychiatry and Clinical Neuroscience*, **15**, 423–430.
- Parkinson Study Group (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *New England Journal of Medicine*, **340**, 757–763.
- Rascol, O., Goetz, C., Koller, W., *et al* (2002) Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet*, **359**, 1589–1598.
- Ring, H. A. & Serra-Mestres, J. (2002) Neuropsychiatry of the basal ganglia. *Journal of Neurology, Neurosurgery and Psychiatry*, **72**, 12–21.
- Schoenfeld, M., Myers, R. H. & Cupples, L. A. (1984) Increased rate of suicide among patients with Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 1283–1287.
- Schreurs, K. M., de Ridder, D. T. & Bensing, J. M. (2002) Fatigue in multiple sclerosis: reciprocal relationships with physical disabilities and depression. *Journal of Psychosomatic Research*, **53**, 775–781.
- Schwartz, J. M. & Marsh, L. (2000) The psychiatric perspectives of epilepsy. *Psychosomatics*, **41**, 31–38.
- Siegert, R. J. & Abernethy, D. A. (2005) Depression in multiple sclerosis: a review. *Journal of Neurology, Neurosurgery and Psychiatry*, **76**, 469–475.
- Simpson, G. & Tate, R. (2005) Clinical features of suicide attempts after traumatic brain injury. *Journal of Nervous and Mental Disease*, **193**, 680–685.
- Stenager, E. N., Stenager, E., Koch-Henricksen, N., *et al* (1992) Suicide and multiple sclerosis: an epidemiological investigation. *Journal of Neurology, Neurosurgery and Psychiatry*, **55**, 542–545.
- Stenager, E. N., Madsen, C., Stenager, E., *et al* (1998) Suicide in patients with stroke: epidemiological study. *BMJ*, **316**, 1206.
- Teasdale, T. W. & Engberg, A. W. (2001) Suicide after traumatic brain injury: a population study. *Journal of Neurology, Neurosurgery and Psychiatry*, **71**, 436–440.
- Tranel, D., Bechara, A. & Damasio, A. R. (2000) Decision making and the somatic marker hypothesis. In *The New Cognitive Neurosciences* (ed. M. S. Gazzaniga), pp. 1047–1061. Cambridge, MA: MIT Press.
- Turner-Stokes, L. & Hassan, N. (2002) Depression after stroke: a review of the evidence base to inform the development of an integrated care pathway. Part 2: Treatment alternatives. *Clinical Rehabilitation*, **16**, 248–260.
- Vataja, R., Leppavuori, A., Pohjasvaara, T., *et al* (2004) Poststroke depression and lesion location revisited. *Journal of Neuropsychiatry and Clinical Neuroscience*, **16**, 56–62.
- Weigell-Weber, M., Schmid, W. & Spiegel, R. (1996) Psychiatric symptoms and CAG expansion in Huntington's disease. *American Journal of Medical Genetics*, **67**, 53–57.
- Witjes-Ané, M.-N., Vegter-van der Vlis, M., van Vugt, J., *et al* (2003) Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. *Journal of Neuropsychiatry and Clinical Neuroscience*, **15**, 7–16.

MCQs

1 In traumatic brain injury:

- the best predictor of outcome is the period of post-trauma amnesia
- late-onset agitation predicts long-term aggression
- aggression and agitation respond differently to medication
- suicidality has no association with hopelessness
- there is evidence of an association with schizophrenia.

2 Suicide rates have been shown to be higher in people with:

- Huntington's disease
- hedonistic homeostatic dysregulation
- traumatic brain injury
- REM sleep behaviour disorder
- stroke.

3 Research and investigations into sleep disorders have suggested that:

- hypocretins can be differentiated from orexins as having a role in sleep and arousal
- there is an HLA association with REM sleep behaviour disorder
- sleep latency of more than 10 min on overnight polysomnography is characteristic of narcolepsy
- clonazepam is the first-line treatment for narcolepsy
- REM sleep behaviour disorder can precede future movement disorders.

4 In Parkinson's disease:

- psychosis is associated with decreases in anti-parkinsonian medications
- clozapine is an appropriate treatment of psychotic symptoms
- hypersexuality, hypomania and pathological gambling can be seen with increased doses of dopamine-replacement medications
- dementia should be treated with rivastigmine as there is randomised controlled trial evidence in favour of this
- tricyclic antidepressants worsen motor symptoms.

5 People with epilepsy:

- a should not be given psychotropic medications as they increase mean seizure frequency
- b when treated with carbamazepine can be given fluoxetine without monitoring of serum levels
- c can also have non-epileptic seizures
- d as well as non-epileptic seizures need a lumbar puncture to ascertain prolactin levels for diagnostic purposes
- e taking tricyclics may be more likely to experience a reduction in seizure threshold than those taking SSRIs.

MCQ answers				
1	2	3	4	5
a T	a T	a F	a F	a F
b F	b F	b F	b T	b F
c F	c T	c F	c T	c T
d F	d F	d F	d F	d F
e T	e T	e T	e F	e T

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