REVIEW ARTICLE

CNS Drugs 2008; 22 (8): 631-644
1172-7047/08/0008-0631/$48.00/0

Delirium and its Treatment

Azizah Attard, *Gopinath Ranjith* and *David Taylor*

Pharmacy Department and Psychiatric Liaison Services Department, South London and Maudsley NHS Foundation Trust, London, England

Contents

Abstract

Delirium occurs at rates ranging from 10% to 30% of all hospital admissions. It is a negative prognostic indicator, often leading to longer hospital stays and higher mortality. The aetiology of delirium is multifactorial and many causes have been suggested. The stress-diathesis model, which posits an interaction between the underlying vulnerability and the nature of the precipitating factor, is useful in understanding delirium.

Preventing delirium is the most effective strategy for reducing its frequency and complications. Environmental strategies are valuable but are often underutilized, while remedial treatment is usually aimed at specific symptoms of delirium. Antipsychotics are the mainstay of pharmacological treatment and have been shown to be effective in treating symptoms of both hyperactive and hypoactive delirium, as well as generally improving cognition. Haloperidol is considered to be first-line treatment as it can be administered via many routes, has fewer active metabolites, limited anticholinergic effects and has a lower propensity for sedative or hypotensive effects compared with many other antipsychotics. Potential benefits of atypical compared with typical antipsychotics include the lower propensity

to cause over-sedation and movement disorder. Of the second-generation antipsychotics investigated in delirium, most data support the use of risperidone and olanzapine. Other drugs (e.g. aripiprazole, quetiapine, donepezil and flumazenil) have been evaluated but data are limited.

Benzodiazepines are the drugs of choice (in addition to antipsychotics) for delirium that is not controlled with an antipsychotic (and can be used alone for the treatment of alcohol and sedative hypnotic withdrawal-related delirium). Lorazepam is the benzodiazepine of choice as it has a rapid onset and shorter duration of action, a low risk of accumulation, no major active metabolites and its bioavailability is more predictable when it is administered both orally and intramuscularly.

Since the time of Hippocrates, a presentation similar to delirium, phrenitis, has been described, differentiating it from other disorders such as melancholia and mania.[1] In spite of this long history, delirium is often an overlooked syndrome in medically ill patients.[1] This may be because delirium is a syndrome that is usually caused by a medical condition or surgical intervention, but presents with cognitive and behavioural symptoms, thus failing to be owned by any speciality.

Often described as acute confusional states or organic brain syndrome, delirium is the current accepted universal term. Controversy continues as to what is the basic defect in delirium. It has variously been conceptualized as a disorder of attention, the sleep-wakefulness cycle, consciousness or global cognitive function.[1] In fact, it may be best described as acute brain dysfunction analogous to acute renal failure or respiratory failure.

1. Epidemiology

1.1 Prevalence and Incidence

Wide variations in the rates of delirium occurrence have been reported in the literature, mainly as a result of differences in the setting, methodology, instruments used to measure delirium, and the professional background and training of the assessors. A recent systematic review that included 21 studies examining the prevalence of delirium at admission, offers the most comprehensive evidence of epidemiology and found rates ranging from 10% to 30%.[2]

1.2 Course and Outcome

Delirium is a negative prognostic indicator in hospitalized patients, often leading to longer hospital stays and higher mortality.[3-5] A recent review reported death rates from 14.5% to 37%.[2] In terms of the clinical course of delirium, the evidence shows significant rates of ongoing delirium once patients have been discharged from hospital. Rates of persistent delirium have been reported in 32% of patients at the time of hospital discharge, 32% of patients at 6 months following discharge and 41% of patients at 1 year following discharge.[6,7] The same prospective study also found that delirium was an independent predictor of poor cognitive and functional status during the year following medical admission.[8] Delirium at discharge is associated with high rates of nursing home placements.[9]

1.3 Risk Factors

The aetiology of delirium is multifactorial. Exhaustive lists exist of possible causes of delirium that encompass most known diseases in medicine. More useful in understanding delirium is the stress-diathesis model, which posits an interaction between the underlying vulnerability and the nature of the insult (or precipitating factor). For example, in an already vulnerable individual, such as someone with established dementia, a minor factor, such as the prescription of a hypnotic, could trigger delirium, while in a healthy individual it would need a massive insult such as major surgery to do so.[10]

Risk factors that interact with baseline vulnerability to predict delirium can be divided into predisposing and precipitating factors. Predisposing factors include visual impairment, severe medical ill-

ness, cognitive impairment and altered blood urea : creatinine ratio. These can help to identify high-risk patients or to identify factors that need to be addressed at admission. Other identified predisposing factors include increasing age, male gender, lower educational attainment, presence of dementia and other neurological disorders, depression, and the severity, burden of co-morbidity and functional impairments associated with the primary physical illness.[11-15] In considering age as a predisposing factor, it has recently been argued that rather than consider biological age, concepts such as physiological age or frailty may be more important.[12] Precipitating factors include the use of physical restraints, malnutrition, the addition of three or more medications in the previous 24 hours, use of a bladder catheter, and any iatrogenic event.[11,12] Other precipitating factors include sedating medications, medications with anticholinergic effects, illicit substance withdrawal, severe acute illness, infections, organ failure, fluid and electrolyte imbalance, hypoperfusion states, and urinary and faecal retention.[13,16-18] Environmental precipitants such as the nature of the intensive care unit, lack of orienting objects (clock, calendar, etc.) and a low level of social interactions may also be important.

2. Phenomenology

2.1 Symptoms

Diagnosis of delirium according to the International Classification of Diseases-10th edition (ICD-10)[19] requires symptoms in each of the following areas:

- impairment of consciousness and attention;
- global disturbance of cognition (including illusions, hallucinations, delusions and disorientation);
- psychomotor disturbances;
- disturbance of the sleep-wake cycle;
- emotional disturbances.

Diagnosis of delirium according to the DSM-IV[20] requires:

- disturbance of consciousness and attention;
- change in cognition (including memory deficit, disorientation or language disturbance);
- development of a perceptual disturbance.

Both schedules emphasize a rapid onset and fluctuating course, and both require that the disturbance is caused by the direct consequences of a general medical disorder. Other symptoms include disturbances in memory, reading, writing and emotions. The level of activity and alertness of the patient allows for the division of delirium into three different subtypes – hypoactive, hyperactive and mixed. From a clinical perspective, the importance of subtyping on the aetiology or prognosis of delirium remains uncertain.[21-25]

3. Assessment

3.1 Clinical Assessment

Clinical assessment of delirium involves taking a detailed medical and psychiatric history of the patient, which includes a thorough medical, neurological and mental state examination. Commonly used cognitive screening tools such as the Mini-Mental State Examination, Abbreviated Mental Test and Clock Drawing Test may help in detecting cognitive deficits; however, these screening tools are not specific for delirium.[26,27] Investigations such as an EEG, while not essential in the diagnosis, may be helpful in identifying changes associated with encephalopathy and in ruling out nonconvulsive status epilepticus. Neuroimaging is not routinely indicated but may have a role in determining the diagnosis if neurological pathology is suspected.

3.2 Assessment Instruments

The instruments developed to detect and assess delirium range from semi-structured interview schedules to checklists. A few of the most widely used instruments are described in this section.

3.2.1 Delirium Symptom Interview

The Delirium Symptom Interview is a 34-item interview protocol that assesses seven symptom domains from the DSM-III[28] criteria for delirium. It has good psychometric properties and can be used by lay interviewers.[29]

3.2.2 Delirium Rating Scale

The Delirium Rating Scale (DRS) is a 10-item clinician-rated symptom rating scale.[30] The items were chosen on the basis of literature review and

DSM-III[28] criteria. It can be used to rate the severity of symptoms and monitor response to treatment. The DRS-Revised-98 (DRS-R-98) was described by the same group as an improvement on the DRS.[31] It contains 16 items, 13 of which refer to symptoms and signs of delirium plus three optional items referring to temporal onset of symptoms, fluctuation of symptoms and the underlying physical disorder. It is designed to be rated by physicians and psychiatrists, and can be used both as a diagnostic tool and a measure of severity.

3.2.3 Confusion Assessment Method

The Confusion Assessment Method (CAM) is perhaps the most widely used tool for identification of delirium, both in research and clinical practice.[32] Developed by an expert panel through a consensus-building process, the instrument consists of nine criteria from the DSM-III-R.[33] There is an accompanying algorithm that can be used to make a diagnosis of delirium. A modification of the CAM for use in intensive care units, the CAM-ICU, has also been recently described.[34]

3.2.4 Memorial Delirium Assessment Scale

The Memorial Delirium Assessment Scale is a clinician-administered scale chiefly used in rating the severity of delirium in cancer patients.[35]

4. Literature Search

The MEDLINE (January 1966 to December 2007), EMBASE (January 1980 to December 2007) and Cochrane (to December 2007) databases were searched for English language articles using the keywords 'delirium', 'acute confusional states', 'confusional state' and 'drug treatment'.

As delirium is often a transient disorder, the condition of many individuals improved as their underlying medical condition was treated, without the need for pharmacological management of delirium. Clinical trials that looked at the efficacy of treatment were often not placebo-controlled, were run over a short duration or had a very small sample size. In a recent Cochrane review on antipsychotics for delirium, only three trials were deemed acceptable for inclusion in the review.[36] Therefore, the current authors felt that a broad inclusion criteria would allow for a larger scope to be covered, and all studies and case reports were included. The final articles chosen were original research articles and those that included details such as drug route, dose and drug effect.

5. Management

Preventing delirium is the most effective strategy for reducing both its frequency and the complications associated with this disorder.[3] Interventions aimed at reducing the effects of some of the common causes of delirium, which include reducing sensory deficits, immobility, sleep disturbance, dehydration and cognitive impairment, often reduce the number and duration of delirium episodes.[37-40]

Environmental strategies are under-utilized and are often only applied in response to behavioural disturbance rather than in response to the degree of cognitive impairment.[37,41] Table I summarizes supportive and environmental strategies that have been shown to be effective in the overall care of patients with delirium.

Rationalizing all prescribed medications remains a useful intervention in the management of delirium.[44] Most prescribed medications can cause delirium, but benzodiazepines and drugs with anticholinergic properties have a particular propensity.[45,46] Elderly people are more vulnerable to the adverse effects of medications, even at low doses, and are particularly at risk of developing delirium when more than three medications are commenced during a hospital admission.[47]

The effectiveness of prophylactic pharmacological treatment of delirium in high-risk populations has not been fully established. A study to assess the use of preoperative pharmacological treatment to prevent postoperative delirium has not been shown to reduce the incidence of delirium, but did have a positive effect on the duration and severity of this disorder.[48]

Managing postoperative pain has also been shown to be an independent strategy in preventing postoperative delirium and is in fact more important than the type of anaesthesia and type of opioid analgesic used.[49]

Table I. Supportive and environmental strategies to manage delirium[41-43]

Providing support and orientation
Communicate clearly and concisely: give repeated verbal reminders of the day, time and location, and identify key individuals, such as members of the treatment team and relatives
Provide clear signposts to patient's location, including clock, calendar, chart with the day's schedule
Have familiar objects from the patient's home in the room
Ensure consistency in staff (for example a key nurse)
Use a television or radio for relaxation and to help the patient maintain contact with the outside world
Involve family and caregivers to encourage feelings of security and orientation
Avoid physical restraints, if possible, as they often increase agitation. If restraint is unavoidable, observe appropriate guidelines
Providing an unambiguous environment
Simplify care area by removing unnecessary objects; allow adequate space between beds
Consider using single rooms to aid rest and avoid extremes of sensory experience
Do not frequently change the patient's bed location
Avoid using medical jargon in front of the patient as it may encourage paranoia
Ensure that lighting is adequate; provide a 40–60 W night light to reduce misperceptions
Control sources of excess noise (such as staff, equipment, visitors): aim for <45 decibels in the day and <20 decibels at night
Keep room temperature between 21°C and 23.8°C
Maintaining competence
Identify and correct sensory impairments: ensure patients have their glasses, hearing aid and dentures
Consider an interpreter if needed
Encourage self care and participation in treatment (for example have the patient give feedback on pain)
Arrange treatments to allow for maximum periods of uninterrupted sleep
Maintain activity levels

6. Pharmacological Treatment of Delirium

Pharmacological treatment should be reserved for patients whose symptoms of delirium would threaten their own safety or the safety of others, or would result in the interruption of essential therapy.[3] The use of psychotropic drugs complicates the ongoing mental state assessment, can impair the patient's ability to understand and therefore cooperate with treatment, and is associated with a greater risk of falls in the elderly population. Common errors in managing delirium are to overuse benzodiazepines and to use antipsychotic medications in excessive doses or to administer them too late.[50]

Treatment is usually aimed at specific symptoms of delirium and efforts should be made to identify and treat underlying causes.[51]

Some general principles when prescribing medication for the treatment of delirium are as follows:[50-54]

- use one drug at a time;
- keep the use of sedatives and antipsychotics to a minimum;
- tailor dose according to age, body size and degree of agitation;
- titrate dose to effect;
- increase scheduled doses if regular 'as needed' doses are required;
- all medication should be reviewed at least every 24 hours;
- medicines are usually discontinued 7–10 days after symptoms resolve.

6.1 Antipsychotic Drugs

Antipsychotics are the cornerstone of pharmacological treatment and have been shown to be effective in treating symptoms of both hyperactive and hypoactive delirium, as well as generally improving cognition (table II).[37,55-57]

6.1.1 Typical Antipsychotics

As haloperidol can be administered by intravenous, intramuscular or oral routes, coupled with the fact that there is more experience with this antipsychotic, it remains the first-line treatment in many clinical guidelines.[52,58] A Cochrane Review and a recent systematic review on the use of antipsychotics in delirium concluded that there is no evidence of a differential effect of low-dose haloperidol compared with risperidone on the overall control of delirium.[36,83] Furthermore, the incidence of adverse effects for olanzapine and risperidone were comparable to those for low-dose haloperidol.[83]

Haloperidol has fewer active metabolites, limited anticholinergic effects and has a lower propensity for sedative or hypotensive effects compared with many other antipsychotics.[55] The actual haloperidol dose needed to exert maximum effect is under debate, with most authors recommending 1–2 mg

Table II. Drugs that have been used in the treatment of delirium

Drug	Dosage	Notable adverse effects	Notes
Typical antipsychotics	See individual medications		
Haloperidol[3,5,39,52,58]	**PO:** 1–2 mg every 2–4 h In acute delirium, a loading dose of 2 mg may be administered first Usual maximum of 10 mg/day[59] Peak effect: 4–6 h In the elderly, these doses are halved	EPSEs can occur, particularly at doses >3 mg	Considered first-line agent Haloperidol has been proven to be useful in the treatment of both hypoactive and hyperactive delirium Use cautiously in the withdrawal of alcohol or sedative hypnotics Avoid in anticholinergic toxicity, hepatic failure or neuroleptic malignant syndrome Avoid in Lewy body dementia
	IM/IV: 0.5–1 mg. Observe for 30–60 min and repeat if necessary Peak effect: 20–40 min In the elderly, these doses are halved Usual maximum of 5 mg/day[59]	IV administration is associated with a lower incidence of EPSEs but a higher risk of prolonged QTc interval	ECG monitoring is essential
Chlorpromazine[55,60]	Starting doses of 12.5–25 mg PO stat	Chlorpromazine is very rarely used parenterally because of local irritation	Chlorpromazine is not recommended in hypoactive delirium because it causes excessive sedation
Droperidol[55,60]	Starting dose of 2 mg PO stat Available as a parenteral formulation	Be aware of excess sedation, hypotension and the risk of prolongation of the QTc interval	Droperidol is not recommended in hypoactive delirium because it causes excessive sedation. No longer available in the UK
Atypical antipsychotics	See individual medications	EPSEs generally occur at a lower rate with atypical antipsychotics than with haloperidol Anticholinergic adverse effects are still possible with atypical antipsychotics	Less experience with the use of atypicals in delirium compared with haloperidol Very few atypical antipsychotics exist as a rapid-acting injection, thus limiting their use. In terms of oral formulations, most experience is with risperidone and olanzapine Atypical antipsychotics may be considered in patients who have previously experienced haloperidol-induced EPSEs

Continued next page

Table II. Contd

Drug	Dosage	Notable adverse effects	Notes
Olanzapine[61-69]	2.5–5 mg od PO Usual maximum 20 mg/day Available as a rapid-acting IM injection	See atypical antipsychotics (above) May cause over-sedation	Intramuscular olanzapine has not been assessed for the treatment of delirium May be useful for sleep-wake cycle disorder
Risperidone[61-69]	0.5 mg bid PO, with additional doses every 4-hourly as needed Usual maximum 4 mg/day Available as a long-acting IM injection	See atypical antipsychotics (above) May cause sedation, nausea and mild parkinsonism	The long-acting injection is inappropriate for the treatment of delirium as it takes a long time to reach steady state
Quetiapine[70]	12.5–25 mg od PO This may be increased every 1–2 days to a maximum of 200 mg/day if it is well tolerated In older patients, dosages are rarely >50 mg/day	See atypical antipsychotics (above) May cause over-sedation	May be useful for sleep-wake cycle disorder
Amisulpride[70]	50–300 mg od PO Maximum of 800 mg/day	See atypical antipsychotics (above)	Very limited evidence
Aripiprazole[71,72]	5–15 mg/day PO Maximum of 30 mg/day	See atypical antipsychotics (above)	Very limited evidence
Ziprasidone[73,74]	10 mg every 2 hours IM Usual maximum 40 mg/day	Prolongation of QTc interval limits its use and ECG monitoring is essential	Very limited evidence
Benzodiazepines	See individual medications		
Lorazepam[5,60]	0.5–1 mg every 2–4 hours as needed PO/IM Usual maximum 4 mg in 24 h IV use is usually reserved for emergencies	More likely to cause respiratory depression, over-sedation and paradoxical excitement than antipsychotics Prolongation and worsening of delirium symptoms has been demonstrated in clinical trials	Considered first-line treatment in alcohol or sedative hypnotic withdrawal, Parkinson's disease and neuroleptic malignant syndrome. Lorazepam is usually the preferred benzodiazepine as it has no active metabolites and is able to be administered parenterally

Continued next page

Table II. Contd

Drug	Dosage	Notable adverse effects	Notes
Diazepam[39]	Starting dose of 5–10 mg PO stat In the elderly, a starting dose of 2 mg is recommended	Much longer half-life compared with lorazepam; therefore, diazepam is the preferred drug in the treatment of alcohol withdrawal Prolongation and worsening of delirium symptoms has been demonstrated in clinical trials	Used in alcohol or sedative hypnotic withdrawal, Parkinson's disease and neuroleptic malignant syndrome
Oxazepam[47]	15–30 mg PO stat	Prolongation and worsening of delirium symptoms has been demonstrated in clinical trials	Shorter acting agent compared with diazepam, but is the preferred drug in the presence of hepatic insufficiency
Midazolam[47]	1.25 mg IM stat starting dose	Absorption from IM dose can be unpredictable, limiting its use	This agent has largely been used in palliative care and acute agitation
Other agents	See individual medications		
Flumazenil[75]	1–2 mg stat by slow IV bolus over 10 min	Nausea and vomiting	Very limited experience Tried in patients with hepatic encephalopathy or organ damage to temporarily reverse delirious state in the hope that the patient can participate in consent to treatments
Melatonin[76,77]	2 mg od PO	Very rarely increases risk of seizures	Very limited experience, mainly used to correct altered sleep-wake cycle
Ondansetron[61]	8 mg od PO	QTc interval prolongation has been reported Constipation and headache can occur	Limited experience, has only been used in post-cardiac surgery settings
Trazodone[78]	25–150 mg at night PO	Over-sedation is problematic	Limited experience, used only in uncontrolled studies

Continued next page

Table II. Contd

Drug	Dosage	Notable adverse effects	Notes
Donepezil[79]	5 mg od PO	Diarrhoea, fatigue and muscle cramps	Limited experience, used only in case reports, largely in patients with hypoactive delirium or Lewy body dementia
Rivastigmine[80,81]	3–9 mg od PO	Nausea, vomiting, loss of appetite and diarrhoea are common adverse effects	Limited experience, only used in small, retrospective cohort studies Usually used in chronic delirium as an adjunct to antipsychotics, or in Lewy body dementia
Valproic acid[82]	Starting dosage of 250 mg bid PO, increased to reach a plasma concentration of 50–100 mg/L	Contraindicated in active liver disease Nausea, vomiting, gastralgia and diarrhoea are common adverse effects	Some case reports of its use in patients in whom antipsychotics and/or benzodiazepines were ineffective

bid = twice daily; **EPSE** = extrapyramidal side effects; **IM** = intramuscular; **IV** = intravenous; **od** = once daily; **PO** = oral; **QTc** = corrected QT; **stat** = at once.

of oral haloperidol every 2–4 hours when required.[37,55,56] The maximum daily dose of haloperidol has achieved less consensus in the literature. The 53rd edition of the British National Formulary[84] recommends 18 mg as a maximum daily intramuscular and intravenous dose, and 30 mg as a maximum daily oral dose for adults. In case reports, up to 50 mg/day of haloperidol has been used intravenously with minimal effects on heart rate, respiratory rate, blood pressure and pulmonary artery pressure, as well as minimal extrapyramidal adverse effects.[85] In a survey of 912 healthcare professionals on the management of delirium, more than one-half of the responders reported giving haloperidol <10 mg/day, with the median dosage reported as 30 mg/day.[59] It is important to bear in mind that, generally, the elderly population need lower doses.

Generally, intravenous use of haloperidol is associated with a lower incidence of extrapyramidal adverse effects but a higher risk of developing Torsades de pointes.[85,86] Therefore, patients receiving intravenous haloperidol should receive ECG monitoring.[39,58,84] More recently, the UK Summary of Product Characteristics[84] for the oral formulation of haloperidol has also highlighted the need for ECG monitoring in patients receiving haloperidol by any route. A QTc interval >500 ms would suggest a need to stop haloperidol and prompt an immediate referral to a cardiologist.[61,87] QTc intervals >440 ms in men or >470 ms in women but <500 ms should prompt a repeat ECG and the clinician should consider referral to a cardiologist.[87]

Chlorpromazine, droperidol and pimozide have all been used in the treatment of hyperactive delirium.[55,88] Levomepromazine and chlorpromazine have been used for very agitated delirious patients, largely because these drugs are more sedating compared with haloperidol. Both can be administered subcutaneously although few clinicians use any form of parenteral chlorpromazine. Aside from causing pain at the injection site, adverse effects such as excessive sedation and hypotension clearly need to be monitored.[60] Thioridazine and pimozide are no longer routinely used, largely because of their potentially dangerous effect on prolonging the QTc interval.[87]

6.1.2 Atypical Antipsychotics

Potential benefits of atypical compared with typical antipsychotics include the lower propensity to cause over-sedation and extrapyramidal adverse effects (the latter reducing the need for anticholinergic medication, which can worsen symptoms of delirium).[62] Most atypical antipsychotics are only available as an oral formulation, which restricts their use, making it difficult for prescribers to gain experience in using this group of drugs. In trials reviewing the use of atypicals, patients who were not able to swallow were simply excluded from the studies.

There have been concerns surrounding the use of atypical antipsychotics and the increased risk of stroke in the elderly population.[89] However, more recent studies have failed to find any differences in the risk of stroke between patients taking a typical or an atypical antipsychotic.[90,91] Metabolic disturbances induced by the long-term use of atypical antipsychotics, particularly olanzapine and clozapine, have been a major health concern and may affect the choice of drug in delirium.[92] However, the treatment of delirium usually takes place over a short period of time, generally 7–21 days at most, in an inpatient setting where these concerns may be less important.

Most data available relate to risperidone and olanzapine.[61-69] Olanzapine at dosages of 2.5–10 mg/day has been used in the treatment of delirium.[62,66,93,94] Authors have reported choosing olanzapine over other antipsychotics for patients who also have parkinsonism.[94] Olanzapine, through its strong antihistaminergic activity, is sedating. Over-sedation can worsen confusion and interfere with the resolution of delirium, particularly hypoactive symptoms.[38,55,66,88,95] This was demonstrated in a large open-label trial using olanzapine, where the main adverse effect reported was sedation leading to dose reduction.[88] A worsening of delirium was reported in 2 of the 79 patients, leading to discontinuation of olanzapine.[88] On the other hand, this antihistaminergic activity may be beneficial in the regulation of the sleep-wake cycle.[88,96,97] Olanzapine is available as an oral formulation and as a rapid-acting intramuscular injection. However, when administering rapid-acting olanzapine injection, there is a requirement to separate its administration from injectable benzodiazepines by 1 hour, which limits both its use and further evaluation for the treatment of delirium.[98]

Risperidone at dosages of 0.5–4 mg/day has been shown to be successful in the treatment of delirium, with the main adverse effects reported as sedation, nausea and mild parkinsonism.[67-69,99,100] Some authors prefer to use risperidone over olanzapine on the basis that risperidone has less propensity for anticholinergic adverse effects, but in clinical practice there is little evidence for a difference between the two drugs.[62,64,66,101] Risperidone is available as both an oral formulation and a long-acting intramuscular formulation. However, the intramuscular formulation is a slow-release preparation, does not establish therapeutic concentrations quickly, is administered every 2 weeks and is therefore of very limited use in delirium.

There are relatively fewer studies relating to the use of quetiapine in delirium. Dosages start at 12.5–25 mg/day, increasing to a mean dosage of between 50 and 200 mg/day. In the elderly population, dosages very rarely exceed 50 mg/day.[62,96,97,102] Serious adverse events, including extrapyramidal adverse effects, were not observed. As quetiapine also has strong antihistaminergic activity, it is sedating and can therefore potentially worsen confusion but provide benefit in the regulation of the sleep-wake cycle. One patient in a small pilot trial (n = 22) developed excessive sedation and worsening delirium, leading to the eventual discontinuation of quetiapine.[102]

A small (n = 31) randomized, open-label, prospective study examined the use of amisulpride compared with quetiapine for the treatment of delirium.[70] The mean dosage of amisulpride was 156.4 mg/day, and that of quetiapine was 113 mg/day.[70] There was no remarkable difference in outcome between the two treatment groups and it seemed that amisulpride produced a similar effect on sleep as quetiapine.

Aripiprazole, the newest atypical antipsychotic, has been used in a number of case reports for the treatment of delirium.[71,72] Dosages used vary from 5 mg/day to 30 mg/day. Aripiprazole may have a unique role in the treatment of hypoactive delirium because of its less sedating properties compared with other antipsychotics; this role has yet to be proven. In fact, in some of the reported cases, seda-

tion was found to be the only remarkable adverse effect.[72]

A small number of reports describe the successful use of ziprasidone in the treatment of delirium;[73,74] however, changes in the QTc interval have inevitably limited its use. ECG monitoring is essential with this drug.

6.2 Benzodiazepines

Benzodiazepine use in delirium requires careful consideration as this class of drugs has the disadvantage of potentially aggravating delirium, particularly in patients with dementia.[18] They appear to be less effective than antipsychotics when used as sole agents and are more likely to cause over-sedation, exacerbation of confusion, and respiratory suppression.[38,39] In an ICU setting, a study has found that the use of sedatives and analgesics, particularly lorazepam, plays a dose-related temporal role in contributing to a patient's transition to delirium.[18]

Benzodiazepines remain the mainstay of treatment in alcohol and sedative hypnotic withdrawal-related delirium. They can also be a useful adjunct for the treatment of patients who cannot tolerate antipsychotic medications. Some authors suggest a trial of adding benzodiazepines to antipsychotic therapy when delirium does not respond to antipsychotics alone.[5,60]

Of the benzodiazepines, lorazepam has several advantages over the others as it has a rapid onset and shorter duration of action, a low risk of accumulation, has no major active metabolites and its bioavailability is more predictable when administered both orally and intramuscularly.[5,60]

6.3 Alternative Therapies

Used in low doses, the antidepressants trazodone and mianserin have been found to reduce noncognitive symptoms of delirium independent of the mood-altering actions of the drug.[78,103] Ondansetron, a specific serotonin antagonist, used in dosages of 8 mg/day, has been shown to be useful in post-cardiac surgery delirium in a study involving 35 patients.[61] The reported positive response to these medications indirectly suggest a role for serotonin in symptoms of delirium.

Delirium can impair a patient's decision-making ability. A novel approach to address this is to use aggressive treatment to temporarily reverse delirious states to restore a patient's capacity to consent to treatment.[75] A temporary approach such as this is important when delirium cannot be permanently reversed without extremely invasive treatments such as organ transplantation or valve replacement.[75] Intravenous flumazenil, in total dosages from 1 to 2 mg/day, has been used successfully in a small number of patients.[75] The proposed mechanism was GABA antagonism, temporarily reducing GABAergic tone and thus lifting sedation.[75]

Disruption of the sleep-wake cycle after surgery can occur as a result of increased cortisol secretion and a decrease in serum melatonin levels.[76] Melatonin in dosages of up to 2 mg/day has been used to treat severe postoperative delirium unresponsive to antipsychotics or benzodiazepines.[77]

A small trial (n = 33) assessing donepezil, an anticholinesterase, in postoperative delirium after elective total hip replacement found that this drug did not significantly reduce the incidence of delirium or length of hospital stay.[104] However, reports also exist of successful treatment of delirium and delirium-like symptoms of Lewy body dementia with donepezil at dosages of 5 mg/day, with maximum effects seen in 4–5 days.[42,79,105] Another anticholinesterase agent, rivastigmine 3–9 mg/day, has been successfully used as an adjunct to antipsychotics in the treatment of chronic delirium.[80,81] The main notable adverse effects were nausea, vomiting, loss of appetite and diarrhoea. Further studies are needed to identify patients whose delirium symptoms are best treated by addressing cholinergic deficiency.

There are also case reports of the successful use of valproic acid in the treatment of delirium in patients in whom antipsychotics and/or benzodiazepines were ineffective.[82] Nausea, vomiting, gastralgia and diarrhoea are common adverse effects of this drug.

7. Conclusion

Delirium is a negative prognostic indicator in hospitalized patients, often leading to longer hospital stays and higher mortality. Preventing delirium is

the most effective strategy for reducing its frequency and complications. Treatment is usually aimed at specific symptoms of delirium, and efforts should be made to identify and treat underlying causes. If treatment is needed, most experience and evidence supports the use of the typical antipsychotic haloperidol in low doses. Potential exists for the use of atypical antipsychotics, particularly the oral formulations of olanzapine and risperidone, although their use is limited by inexperience. Risperidone is not available in a rapid-acting parenteral formulation and restrictions exist surrounding the use of rapid-acting intramuscular olanzapine in combination with benzodiazepines, further limiting its role in the management of delirium. Benzodiazepines are the treatment of choice in delirium associated with alcohol withdrawal. Other drugs have been used but data relating to their safety and effectiveness are insufficient to allow their clinical use to be recommended.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Taylor has received consultancy fees, honoraria or research funding from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Sanofi-Synthelabo, Janssen-Cilag, Wyeth and Novartis. He has also received royalties from Gaskell Publishing and Informa Healthcare. All other authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Lipowski ZW. Delirium: acute confusional states. Oxford: Oxford University Press, 1990
2. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006; 35 (4): 350-64
3. Inouye SK. Delirium in older persons. N Engl J Med 2006; 354 (11): 1157-65
4. Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. Am J Med 1999; 106 (5): 565-73
5. van Zyl LT, Seitz DP. Delirium concisely: condition is associated with increased morbidity, mortality, and length of hospitalization. Geriatrics 2006; 61 (3): 18-21
6. McAvay GJ, Van Ness PH, Bogardus Jr ST, et al. Older adults discharged from the hospital with delirium: 1-year outcomes. J Am Geriatr Soc 2006; 54 (8): 1245-50
7. McCusker J, Cole M, Dendukuri N, et al. The course of delirium in older medical inpatients: a prospective study. J Gen Intern Med 2003; 18 (9): 696-704
8. McCusker J, Cole M, Dendukuri N, et al. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. CMAJ 2001; 165 (5): 575-83
9. Adamis D, Treloar A, Martin FC, et al. Recovery and outcome of delirium in elderly medical inpatients. Arch Gerontol Geriatr 2006; 43 (2): 289-98
10. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999; 10 (5): 393-400
11. Inouye SK, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993; 119 (6): 474-81
12. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA 1996; 275 (11): 852-7
13. Lindesay J, Rockwood K, Rolfson D. The epidemiology of delirium. In: Lindesay J, Rockwood K, Macdonald A, editors. Delirium in old age. Oxford: Oxford University Press, 2002: 27-50
14. Rockwood K, Hogan DB, MacKnight C. Conceptualisation and measurement of frailty in elderly people. Drugs Aging 2000: 17 (4): 295-302
15. Rolfson D. The causes of delirium. In: Lindesay J. Rockwood K, Macdonald A, editors. Delirium in old age. Oxford: Oxford University Press, 2002: 101-19
16. Mach Jr JR, Dysken MW, Kuskowski M, et al. Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. J Am Geriatr Soc 1995; 43 (5): 491-5
17. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161 (8): 1099-105
18. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006; 104 (1): 21-6
19. World Health Organisation. The ICD-10 classification of mental and behavioural disorders. Geneva: World Health Organisation, 2003
20. Caine E, Fann J. Delirium, dementia and other cognitive disorders. In: American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC; American Psychiatric Association, 1994: 124-7
21. de Rooij SE, Schuurmans MJ, van der Mast RC, et al. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. Int J Geriatr Psychiatry 2005; 20 (7): 609-15
22. Meagher DJ, O'Hanlon D, O'Mahony E, et al. Relationship between etiology and phenomenologic profile in delirium. J Geriatr Psychiatry Neurol 1998; 11 (3): 146-9
23. O'Keeffe ST, Lavan JN. Clinical significance of delirium subtypes in older people. Age Ageing 1999; 28 (2): 115-9
24. Marcantonio E, Ta T, Duthie E, et al. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc 2002; 50 (5): 850-7
25. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992; 161: 843-5
26. Adamis D, Morrison C, Treloar A, et al. The performance of the Clock Drawing Test in elderly medical inpatients: does it have utility in the identification of delirium? J Geriatr Psychiatry Neurol 2005; 18 (3): 129-33
27. Tune L, Carr S, Hoag E, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992; 149 (10): 1393-4
28. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association, 1980
29. Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: an interview for the detection of delirium symptoms

in hospitalized patients. J Geriatr Psychiatry Neurol 1992; 5 (1): 14-21
30. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988; 23 (1): 89-97
31. Trzepacz PT, Mittal D, Torres R, et al. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001; 13 (2): 229-42
32. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113 (12): 941-8
33. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987
34. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001; 29 (7): 1370-9
35. Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997; 13 (3): 128-37
36. Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. Cochrane Database Syst Rev 2007; (3): CD005594
37. Tune L, Carr S, Hoag E, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992; 149 (10): 1393-4
38. Meagher DJ. Delirium: optimising management. BMJ 2001; 322 (7279): 144-9
39. Chan D, Brennan NJ. Delirium: making the diagnosis, improving the prognosis. Geriatrics 1999; 54 (3): 28-42
40. Young J, Inouye SK. Delirium in older people. BMJ 2007; 334 (7598): 842-6
41. Meagher DJ, O'Hanlon D, O'Mahony E, et al. The use of environmental strategies and psychotropic medication in the management of delirium. Br J Psychiatry 1996; 168 (4): 512-5
42. Gleason OC. Delirium. Am Fam Physician 2003; 67 (5): 1027-34
43. Casarett DJ, Inouye SK. Diagnosis and management of delirium near the end of life. Ann Intern Med 2001; 135 (1): 32-40
44. Gaudreau JD, Gagnon P, Roy MA, et al. Association between psychoactive medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005; 46 (4): 302-16
45. Anthony JC, LeResche L, Niaz U, et al. Limits of the 'mini-mental state' as a screening test for dementia and delirium among hospital patients. Psychol Med 1982; 12 (2): 397-408
46. Patten SB, Williams JV, Petcu R, et al. Delirium in psychiatric inpatients: a case-control study. Can J Psychiatry 2001; 46 (2): 162-6
47. Moran JA, Dorevitch MI. Delirium in the hospitalised elderly. Aust J Hosp Pharm 2001; 31 (1): 35-40
48. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005; 53 (10): 1658-66
49. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006; 102 (4): 1267-73
50. Nayeem K, O'Keeffe S. Delirium. Clin Med 2003; 3 (5): 412-5
51. Tauscher J, Tauscher-Wisniewski S, Kasper S. Treatment of patients with delirium [letter]. Am J Psychiatry 2000; 157 (10): 1711
52. Potter J, George J. The prevention, diagnosis and management of delirium in older people: concise guidelines. Clin Med 2006; 6 (3): 303-8
53. Schwartz TL, Masand PS. The role of atypical antipsychotics in the treatment of delirium. Psychosomatics 2002; 43 (3): 171-4
54. Meagher D. Delirium: the role of psychiatry. Adv Psychiatr Treat 2001; 7 (6): 433-42
55. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996; 153 (2): 231-7
56. Platt MM, Breitbart W, Smith M, et al. Efficacy of neuroleptics for hypoactive delirium. J Neuropsychiatry Clin Neurosci 1994; 6 (1): 66-7
57. Leentjens AF, van der Mast RC. Delirium in elderly people: an update. Curr Opin Psychiatry 2005; 18 (3): 325-30
58. American Psychiatric Association. Practice guideline for the treatment of patients with delirium. Am J Psychiatry 1999; 156 (5 Suppl.): 1-20
59. Ely EW, Stephens RK, Jackson J, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med 2004; 32 (1): 106-12
60. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med 2004; 18 (3): 184-94
61. Bourgeois JA, Seritan A. Diagnosis and management of delirium. Continuum 2006; 12 (5): 15-32
62. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. Palliat Support Care 2005; 3 (3): 227-37
63. Akiskal HS, Akiskal K, Allilaire JF, et al. Validating affective temperaments in their subaffective and socially positive attributes: psychometric, clinical and familial data from a French national study. J Affect Disord 2005; 85 (1-2): 29-36
64. Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004; 30 (3): 444-9
65. Sipahimalani A, Sime RM, Masand PS. Treatment of delirium with risperidone. Int J Geriatr Psychopharmacol 1997; 1 (1): 24-6
66. Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. Psychosomatics 1998; 39 (5): 422-30
67. Liu CY, Juang YY, Liang HY, et al. Efficacy of risperidone in treating the hyperactive symptoms of delirium. Int Clin Psychopharmacol 2004; 19 (3): 165-8
68. Horikawa N, Yamazaki T, Miyamoto K, et al. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. Gen Hosp Psychiatry 2003; 25 (4): 289-92
69. Parellada E, Baeza I, de Pablo J, et al. Risperidone in the treatment of patients with delirium. J Clin Psychiatry 2004; 65 (3): 348-53
70. Lee KU, Won WY, Lee HK, et al. Amisulpride versus quetiapine for the treatment of delirium: a randomized, open prospective study. Int Clin Psychopharmacol 2005; 20 (6): 311-4
71. Straker DA, Shapiro PA, Muskin PR. Aripiprazole in the treatment of delirium. Psychosomatics 2006; 47 (5): 385-91
72. Alao AO, Soderberg M, Pohl EL, et al. Aripiprazole in the treatment of delirium. Int J Psychiatry Med 2005; 35 (4): 429-33
73. Young CC, Lujan E. Intravenous ziprasidone for treatment of delirium in the intensive care unit. Anesthesiology 2004; 101 (3): 794-5
74. Leso L, Schwartz TL. Ziprasidone treatment of delirium. Psychosomatics 2002; 43 (1): 61-2
75. Bostwick JM, Masterson BJ. Psychopharmacological treatment of delirium to restore mental capacity. Psychosomatics 1998; 39 (2): 112-7
76. Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg 2002; 94 (2): 338-9
77. Cronin AJ, Keifer JC, Davies MF, et al. Melatonin secretion after surgery. Lancet 2000; 356 (9237): 1244-5

78. Okamoto Y, Matsuoka Y, Sasaki T, et al. Trazodone in the treatment of delirium. J Clin Psychopharmacol 1999; 19 (3): 280-2

79. Gleason OC. Donepezil for postoperative delirium. Psychosomatics 2003; 44 (5): 437-8

80. Dautzenberg PL, Mulder LJ, Olde Rikkert MG, et al. Adding rivastigmine to antipsychotics in the treatment of a chronic delirium. Age Ageing 2004; 33 (5): 516-7

81. Dautzenberg PL, Mulder LJ, Olde Rikkert MG, et al. Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage. Int J Geriatr Psychiatry 2004; 19 (7): 641-4

82. Bourgeois JA, Koike AK, Simmons JE, et al. Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. J Neuropsychiatry Clin Neurosci 2005; 17 (2): 232-8

83. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. J Clin Psychiatry 2007; 68 (1): 11-21

84. British national formulary. 52nd ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006

85. Menza MA, Murray GB, Holmes VF, et al. Decreased extrapyramidal symptoms with intravenous haloperidol. J Clin Psychiatry 1987; 48 (7): 278-80

86. Sharma ND, Rosman HS, Padhi ID, et al. Torsades de pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998; 81 (2): 238-40

87. Taylor D, Paton C, Kerwin R. The Maudsley prescribing guidelines. 9th ed. London: Informa Healthcare, 2007

88. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002; 43 (3): 175-82

89. Duff G. Atypical antipsychotic drugs and stroke [online]. Available from ULR: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019490.pdf [Accessed 2008 Jun 11]

90. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 2004; 161 (6): 1113-5

91. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 2005; 330 (7489): 445-8

92. Ananth J, Parameswaran S, Gunatilake S. Side effects of atypical antipsychotic drugs. Curr Pharm Des 2004; 10 (18): 2219-29

93. Broadhurst C, Wilson KC, Kinirons MT, et al. Clinical pharmacology of old age syndromes. Br J Clin Pharmacol 2003; 56 (3): 261-72

94. Gupta N, Sharma P, Prabhakar S. Olanzapine for delirium in parkinsonism: therapeutic benefits in lieu of adverse consequences. Neurol India 2004; 52 (2): 274-5

95. Pandharipande P, Jackson J, Ely EW. Delirium: acute cognitive dysfunction in the critically ill. Curr Opin Crit Care 2005; 11 (4): 360-8

96. Sasaki Y, Matsuyama T, Inoue S, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. J Clin Psychiatry 2003; 64 (11): 1316-21

97. Shinno H, Matsuoka T, Yamamoto O, et al. Successful treatment with quetiapine for delirium in terminally ill cancer patients. Psychogeriatrics 2007; 7 (2): 64-8

98. Eli Lilly & Co. Important safety information reported serious adverse events following use of Zyprexa IM [letter to healthcare professionals]. Eli Lilly and Company Ltd, 2004

99. Gupta N, Sharma P, Mattoo SK. Effectiveness of risperidone in delirium [letter]. Can J Psychiatry 2005; 50 (1): 75

100. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004; 45 (4): 297-301

101. Miyaji S, Yamamoto K, Hoshino S, et al. Comparison of the risk of adverse events between risperidone and haloperidol in delirium patients. Psychiatry Clin Neurosci 2007; 61 (3): 275-82

102. Pae CU, Lee SJ, Lee CU, et al. A pilot trial of quetiapine for the treatment of patients with delirium. Hum Psychopharmacol 2004; 19 (2): 125-7

103. Nakamura J, Uchimura N, Yamada S, et al. Does plasma free-3-methoxy-4-hydroxyphenyl(ethylene)glycol increase in the delirious state? A comparison of the effects of mianserin and haloperidol on delirium. Int Clin Psychopharmacol 1997; 12 (3): 147-52

104. Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry 2007; 22 (4): 343-9

105. Kaufer DI, Catt KE, Lopez OL, et al. Dementia with Lewy bodies: response of delirium-like features to donepezil [letter]. Neurology 1998; 51 (5): 1512

Correspondence: Dr *David Taylor*, Pharmacy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, England.
E-mail: david.taylor@slam.nhs.uk