Case Studies in Psychopharmacology:

The Use of Drugs in Psychiatry

Second edition

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Foreword

It is a great pleasure for me to write a foreword to the revised version of this excellent book. Once again, it comprises an unusual but very practical format. Each of the contributors, all pharmacists with a particular interest in psychopharmacology and drug treatments in psychiatry, provides a typical case history to illustrate an important area of therapeutics. The case history is followed by some focused questions which have been raised by the case history. Answers which incorporate a great deal of pharmacology and practical advice are given to these questions. Key points are then listed and each chapter finishes with a compendious list of references. Some chapters also have suggested further reading.

This formula works very successfully. Although the book cannot claim to be a total account of psychopharmacology, the chapters are chosen with great care, with a particular relevance to practical issues. Difficult problems like the treatment of refractory conditions are evaluated and advice given. Other chapters deal with the side-effects of medication and the measures that could be used to counteract these problems. For example, a chapter on clozapine and its side-effects should enable the practitioner to optimise his or her treatment and also to maintain compliance.

Outside the field of psychosis a whole range of conditions are discussed. The book not only encompasses well-recognised disorders but also cuts across them to deal with the problems of medication and even, as in the case of bipolar disorder, with unlicensed treatments. This exemplifies the 'no-nonsense' approach of the contributors. They have much experience of practical problems of treatment and this is seen in the various chapters.

The contributors discuss each issue in a balanced and clear way. In many areas of drug treatment in psychiatry, opinion is not unanimous. Often, consensus has not yet emerged, reflecting the slow accrual of relevant data. These topics are discussed in a careful way that acknowledges these differences of opinion without confusing the reader completely.

It is hoped that this book, in its second edition, will remain an important addition to the practising psychiatrist's sources of knowledge. Furthermore, it is of interest to pharmacists, especially those specialising in psychiatric conditions. I would hope that reading this book will help other health care workers in the field of psychiatry, such as nurses and social workers. General practitioners with a special interest in managing psychiatric problems will also profit by reading various chapters of particular relevance to them.

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1

Rapid tranquillization

David Taylor

AH, a 38-year-old Caucasian man, was admitted to a locked, acute psychiatric care ward, having been brought in by the police. He was found praying by the side of the road, but became abusive and physically threatening when a policeman approached him. AH was reported to be 'making no sense at all - just talking incoherently about CNN' (the news broadcaster).

On examination, AH was found to be severely thought disordered, with fixed delusions about his role as head of CNN. He wore a hat at all times because it apparently protected him from the 'flat space invaders from CNN' by protecting his brain which 'is like the yolk inside the white, inside the brown'. AH became abusive before any more information could be gained. Having threatened nursing staff, he was restrained and secluded.

In seclusion, AH shouted that he wanted to kill himself and would 'take out anyone who got in

his way'. It transpired that AH had no psychiatric history, but a long forensic record, including GBH, ABH and possession of an offensive weapon. He was taking no medication.

Questions

1. What are the aims of rapid tranquillization (RT)?
2. What place do intramuscular (IM) chlorpromazine and IM zuclopenthixol acetate have in AH's immediate treatment?
3. Are IM atypicals appropriate and effective in RT?
4. Outline a treatment plan for AH. List the safety measures necessary to ensure patient well-being.

Answers

1. What are the aims of rapid tranquillization (RT)?

The principal aim of RT is to reduce suffering and, in doing so, to do no harm to the patient. Secondary considerations include: preventing self harm, preventing harm to others, and reducing the level of expressed emotion in the clinical environment.

RT is used in psychiatric institutions for a variety of reasons. Acutely disturbed or violent behaviour can be a manifestation of many disorders, such as psychosis, substance abuse, stress reactions, dementia, organic disorders (e.g. cerebral tumours) and epilepsy. With such a range of possible precipitants, it is unlikely that any one medication or psychological approach would be suitable for all episodes of violent or disturbed behaviour. It is essential, therefore, to ensure a flexible approach based on diagnosis and circumstance.

In this case, the cause of the psychosis is unknown and a full physical and mental state examination, along with a comprehensive history, should be completed as soon as possible. AH has a history of significant violence to others. His case should be discussed urgently with the local forensic psychiatrist and appropriate placement agreed.

It should also be recognized that prevention of acutely disturbed or violent behaviour (usually by skilled nursing care and appropriate placement) is preferred to the essentially remedial RT. Where RT is required, as it will be even where preventative measures are in place, it is best managed and delivered by an expert or 'emergency' team of clinicians.

2. What place do intramuscular (IM) chlorpromazine and IM zuclopenthixol acetate have in AH's immediate treatment?

Parenteral medication has no place in the immediate management of this patient. The use of parenteral antipsychotics, benzodiazepines and other sedatives should not be seen as first-line options in RT (Kerr and Taylor, 1997).

Initial management should involve the consideration of non-drug methods such as talking down, distraction, and time out seclusion. A full discussion of these methods is beyond the scope of this book [see Beer et al (2001) for further information]. Nevertheless, it is important to recognize that non-drug methods are a humane, safe and often effective treatment for acutely disturbed behaviour.

Depending on diagnosis, oral medication may be appropriate and may be used alongside non-drug measures. With AH, psychosis is evident, although its cause is not known. Oral antipsychotic medication may thus be appropriate and may engender sufficient improvement in the patient for a full history to be taken, and for a mental state and physical examination to be completed. The main danger of using an antipsychotic with AH is that severe dystonia may occur: AH is apparently antipsychotic-naïve. Oral chlorpromazine (100 mg bd or tds) or haloperidol (1–2 mg bd) may be given (note these low, but therapeutic, doses).

Newer, atypical, drugs are probably effective in acute psychosis. The danger of dystonia, parkinsonism and akathisia is minimal, especially if low doses are used. However, the necessity for slow titration with risperidone and quetiapine arguably precludes their use in acute psychosis. Olanzapine 10 mg daily may be suitable and it has sedative properties which may be helpful. Higher doses seem effective and well tolerated (Karagianis et al, 2001). Ziprasidone seems to be

effective in acute psychosis and has anxiolytic effects (Davis and Markham, 1997).

IM chlorpromazine has in the past proved a popular therapy in RT (Cunnane, 1994; Simpson and Anderson, 1996). However, many now do not recommend its use (Kerr and Taylor, 1997). Absorption from IM administration is slow and erratic and varies substantially between individuals (Milton and Jann, 1995). Moreover, IM chlorpromazine can cause profound sedation and hypotension, especially in patients not previously exposed to neuroleptics. There also appears to be a tendency to use very large doses, probably inappropriately (Mannion et al, 1997). In addition, chlorpromazine has a potent effect on cardiac QT interval (Ban and St Jean, 1964). Certainly, IM chlorpromazine is unsuitable for this patient. Indeed, its use in any situation should be actively discouraged.

Zuclopenthixol acetate (Acuphase), a short-acting depot, is also widely used in RT, despite a dearth of supporting literature (Coutinho et al, 1997). Because of the potential for prolonged dystonic reactions, this preparation is unsuitable for neuroleptic-naïve patients. It is also unsuitable for acute treatment. After injection, sedative effects are not apparent for at least two hours and do not peak for 24 hours (Chakravarti et al, 1990). Duration of action is two to three days (Amdisen et al, 1987). Zuclopenthixol acetate is best reserved for patients who otherwise need repeated injections of simple IM or intravenous (IV) formulations. In these situations it is claimed that fewer injections of zuclopenthixol acetate can be given to achieve the same effect as a large number of injections of shorter-acting preparations (Baastrup et al, 1993), although available data would suggest that the administration of additional antipsychotic medication is unlikely to be completely avoided (Fenton et al, 1997).

3. Are IM atypicals appropriate and effective in RT?

Typical antipsychotics have an established place in RT – these drugs are effective antipsychotics in the long term and produce helpful sedative effects in the short term. They may also induce bradykinesia and akinesia, which effectively prevent patients being physically aggressive or dangerous to themselves or others. Conversely, typical antipsychotics in

the doses normally used in RT commonly cause other parkinsonian symptoms, akathisia and, less frequently, dystonia. Indeed, the induction of akathisia may provoke or worsen behavioural disturbance (Siris, 1985; Crowner et al, 1990).

Both ziprasidone (Taylor, 2001) and olanzapine (Jones et al, 2001) have been formulated as IM injections and investigated in RT. Both drugs appear to be at least as effective as haloperidol but with a very limited potential for inducing any extrapyramidal side-effects (EPSEs). It should be noted, however, that the patients treated in randomized controlled trials are far less disturbed than many of those treated in clinical practice and that the efficacy of antipsychotic monotherapy has been evaluated and not the antipsychotic–benzodiazepine combinations used in practice. In addition, a variety of rating scales, none of which has been fully validated for the purpose, have been used to evaluate clinical response. More widespread clinical experience with these preparations is necessary before their place in RT can be properly established.

4. Outline a treatment plan for AH. List the safety measures necessary to ensure patient well-being.

Treatment plan

The following plan is recommended:

- First, try psychological methods, e.g. talking down, time out.
- Offer oral antipsychotic medication.
- If oral medication is refused, parenteral medication should be used if the patient remains severely distressed or is thought liable to cause harm to himself or others.

It is now common practice to give small doses of antipsychotics in combination with benzodiazepines. IV administration is fast-acting and gives 100% bioavailability. It may, however, expose the heart to high concentrations of potentially cardiotoxic drugs - both haloperidol (Metzger and Friedman, 1993) and droperidol (Lischke et al, 1994) have clear dose-related effects on cardiac QT (QTc) interval when given IV. Droperidol has now been withdrawn from use in the UK due to its association with QTc prolongation (Reilly et al, 2000). IM administration is slower-acting with less predictable

absorption but is considered by some to be safer than the IV route.

A suggested regimen is:

Haloperidol *2.5–5 mg IV or IM*
+
Diazepam *5–10 mg IV*

- Benzodiazepines may be used alone where diagnosis is unknown and previous treatment history is not available.
- Promethazine 25–50 mg PO or IM is also an effective sedative.
- Injections may be repeated if necessary after careful assessment – wait 15 minutes after IV injection; 30 minutes after IM injection.
- If the patient improves, offer oral medication.
- If the patient needs repeated injections and has tolerated haloperidol (or alternative) well, consider giving zuclopenthixol acetate (50–150 mg).
- In very rare and extreme circumstances amylobarbitone or paraldehyde may be given. Full discussion with a consultant experienced in the use of these drugs should ALWAYS precede administration. ECT may also be helpful.
- Instant access to ITU facilities should be available.

Measures to ensure safety

- Parenteral procyclidine should be available in case of dystonic reactions.
- Flumazenil should be available to reverse the effects of benzodiazepines should respiratory depression occur. Staff should be familiar with its use.
- Monitoring should include:
  Pulse
  Temperature
  Blood pressure
  Respiratory rate
  Oxygen saturation (by pulse oximeter).
- Electrocardiograph (where available). (Note that training in ECG interpretation for psychiatric trainees is poor (Henderson et al, 1997), and advice should be sought if there is any doubt.)
- Full cardiac/resuscitation facilities should be available, preferably supplied by a 'crash team' in the same hospital.

Key points

- The principal aims of RT are to reduce suffering for the patient and make the environment safe for others.

- With skilled nursing management, only a small proportion of 'incidents' should result in RT.
- Oral medication should be offered first and may be sufficient.
- If the parenteral route is required, either haloperidol 2.5–5 mg and diazepam 5–10 mg IV or lorazepam 1 mg IM are recommended.
- Olanzapine IM and ziprasidone IM show some promise in RT but clinical experience is limited.
- Parenteral chlorpromazine is not recommended.
- Acuphase should never be given to antipsychotic-naïve patients because of its long duration of action, which will make difficult management of any acute dystonic reaction that may occur.
- Routine monitoring after RT should include TPR and BP. ECG monitoring is desirable.

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2

Non-refractory schizophrenia

Carol Paton

SR, a 24-year-old Caucasian man, was brought to casualty by the police after being found wandering amongst the traffic on the local dual carriageway. He was agitated, perplexed and unkempt. Rapport was poor and he muttered to himself around the themes of pollution, overcrowding and confusion. He admitted to second-person auditory hallucinations instructing him to 'organize the streets' and third-person auditory hallucinations which discussed his inability to do so. He exhibited formal thought disorder with knight's move thinking and described passivity phenomena.

SR had suffered from a psychotic episode 14 months previously which involved a three-month admission to hospital. He was treated with fluphenazine depot 50 mg every three weeks and procyclidine 5 mg three times daily and made a good recovery, returning to work in a hotel kitchen. He stopped his depot five months ago and

has had no contact with services since.

SR is the third of four siblings, had a normal birth and achieved normal early milestones, although later underachieved at secondary school. His paternal uncle had a diagnosis of schizophrenia and took his own life.

Physical examination and blood tests were unremarkable and a urine drug screen was negative. The working diagnosis was that of a relapse of a schizophrenic illness.

Questions

1. Describe and explain a typical pharmacological treatment algorithm for schizophrenia. Which drug would be appropriate in this case?
2. What are appropriate treatment doses of the commonly used antipsychotics?
3. What are the short- and long-term benefits of antipsychotics in schizophrenia? Quantify the risks of stopping treatment after recovery.
4. What are the short- and long-term risks of anticholinergics?

Answers

1. Describe and explain a typical pharmacological treatment algorithm for schizophrenia. Which drug would be appropriate in this case?

The quality of clinical trials in schizophrenia is generally poor (Thornley and Adams, 1998). Most recruit small numbers of patients, last for no more than six weeks, are of poor design and use a large number of outcome measures, many of which are of questionable relevance to everyday clinical practice. This results in a poor evidence base on which to construct a treatment algorithm, particularly one that is free from controversy!

Most algorithms now recommend an atypical antipsychotic first line, although some still give the option of an older typical drug. The current edition of the British National Formulary (BNF: 2001) lists 26 different antipsychotic drugs: none is perfect. All (except clozapine) are equally effective in that around 50–60% of patients with

schizophrenia show a meaningful (but often incomplete) response. All antipsychotic drugs have side-effects and these differ both between and within classes. In general, the older drugs cause more extrapyramidal side-effects (EPSEs) and the newer drugs more weight gain. The newer drugs are considerably more expensive. Individual patients perceive side-effects differently and also differ in what they are willing to tolerate: these points are expanded below.

Antipsychotic efficacy is thought to be mediated through D2 blockade in the mesolimbic dopamine pathway in the brain. Conventional antipsychotics, through additional blockade of the nigrostriatal D2 pathway, cause EPSEs in a significant proportion of patients (American Psychiatric Association, 1997), i.e. acute dystonias in 10%, pseudoparkinsonism in 20%, akathisia (which has been linked to aggression and suicidal behaviour) in 20–25% and dysphoria (which is linked to non-compliance and subsequent poor outcome) in a significant proportion (King et al, 1995). Tardive dyskinesia, which can be irreversible, occurs at a rate of around 4% per year of antipsychotic exposure (American Psychiatric Association, 1997).

Anticholinergics can be useful in the treatment of dystonias and pseudoparkinsonism, whereas propranolol or cyproheptadine are more useful in akathisia. Hyperprolactinaemia, due to blockade of the tuberoinfundibular D2 pathway, can result in galactorrhoea, amenorrhoea, gynaecomastia, sexual dysfunction and osteoporosis. Typical antipsychotics also cause, depending on their individual receptor-binding profiles, sedation (H1 block), postural hypotension (adrenergic alpha-1 block) and dry mouth, blurred vision, urinary retention and constipation (muscarinic block). Seizures and neuroleptic malignant syndrome can also occur.

The antipsychotic drugs grouped together under the heading 'atypical' are not homogeneous. The term 'atypical' was originally associated with the inability of a compound to produce catalepsy in laboratory animals (a screening model thought to have good predictive validity in identifying potential antipsychotic agents). Atypical antipsychotics have also been variously defined as having no effect on serum prolactin, improved efficacy against negative symptoms, being highly selective D2 blockers (eg pimozide) or relatively selective for D2 receptors in

mesolimbic areas (eg the withdrawn agent, remoxipride), having a high 5HT2:D2 receptor blocking ratio (eg risperidone, olanzapine) or high intrinsic anticholinergic activity (eg thioridazine). The lack of an accepted standard definition should make it immediately apparent that all atypicals are not the same. Many consider the only true atypical to be clozapine, which is discussed in the chapter on treatment-resistant schizophrenia. For the purposes of this discussion, only the recently introduced antipsychotics, risperidone, olanzapine, quetiapine, zotepine and amisulpride along with sulpiride will be considered broadly to fit the definition of atypicality.

Sulpiride and amisulpride are associated with fewer EPSEs than conventional antipsychotics, but both raise serum prolactin. No studies comparing these two drugs have been published and it is unclear if amisulpride offers any clinical advantages over sulpiride.

Risperidone has been shown in good double-blind placebo-controlled trials to be an effective antipsychotic at a dose of 6 mg daily, although it raises prolactin levels and doses >8 mg daily are associated with an increased incidence of EPSEs (Chouinard et al, 1993). Olanzapine produces very few EPSEs and only a transient rise in prolactin (Tollefson et al, 1997); quetiapine has no effect on prolactin and a very low 'placebo level' incidence of EPSEs.

Zotepine is a 5HT2:D2 blocker that is associated with EPSEs, postural hypotension, sedation and hyperprolactinaemia. It is proconvulsive and associated with QTc prolongation and raised liver function tests (Prakash and Lamb, 1998).

Sertindole, a 5HT2:D2 blocker was withdrawn from the European market in 1998 due to alleged problems with QTc prolongation. It may be available again soon.

While this group of drugs produce significantly fewer dopamine-mediated side-effects than the conventional antipsychotics, weight gain is a significant clinical problem (Taylor and McAskill, 2000) and side-effects due to blockade of other receptors do occur. For example, olanzapine has anticholinergic side-effects and is sedative; risperidone and quetiapine cause postural hypotension significant enough to require that the dose be increased slowly at the start of treatment.

There are arguments in favour of using atypicals first line (Kerwin, 1996), particularly in first-episode schizophrenia, where it is hoped that improved tolerability will lead to an improvement in long-term compliance, and therefore outcome. Objective data in this area are lacking, although a recent study demonstrated that treatment with risperidone led to a higher subjective quality of life than treatment with conventional antipsychotics (Franz et al, 1997).

There are also arguments in favour of using typicals first line. A meta-analysis of randomized controlled trials that included typical and atypical arms (Geddes et al, 2000) concluded that atypicals have no overall efficacy or tolerability advantages over the older drugs (when they are used in doses of no more than 12 mg daily haloperidol or equivalent). When higher doses of typical drugs are used, the atypical is better tolerated. Atypicals are associated with fewer EPSEs than all doses of the older drugs, but the dropout rate from trials is no less than that seen with low-dose typicals. One possible explanation for this finding is that the atypicals have other adverse effects that patients are unwilling to tolerate. A greater propensity to cause weight gain (Taylor and McAskill, 2000) is one such side-effect.

In the majority of patients, schizophrenia is a lifelong illness and long-term treatment with antipsychotic drugs is required. The 'best-fit' antipsychotic should be found for each patient, taking into account their perceptions of, and willingness to tolerate, different side-effects.

If the first antipsychotic is not tolerated, an alternative drug with a different side-effect profile should be tried. Prescribers should familiarize themselves with the differences between drugs. If the patient fails to tolerate or respond to a typical drug, an atypical should be tried and vice versa.

There is little to be gained by substituting one typical drug for another, as a response rate of more than 5% is unlikely (Thompson, 1994). There is no objective evidence that combinations of antipsychotics offer any therapeutic advantage over single agents, although prescribing surveys repeatedly show this to be common practice (eg Ungvari et al, 1997). There is also little to be gained by combining antipsychotics: evidence supporting

such practices is virtually non-existent and co-prescription of typicals with atypicals essentially eliminates any tolerability advantages that atypicals alone might provide (Taylor et al, 2000). (Discussion of the algorithm further than this point for the 30% of patients who are 'treatment resistant' is covered in the chapter on treatment-resistant schizophrenia.)

The patient in this case previously made a good recovery with fluphenazine depot 50 mg every three weeks. His reason for discontinuing treatment is unclear. If side-effects were not the reason, fluphenazine should be prescribed again. Otherwise an alternative antipsychotic with a different side-effect profile should be prescribed as monotherapy, with sedative cover if required early in treatment, provided by a benzodiazepine.

It should be noted that SR had his first episode of psychosis only 14 months ago. Aggressive treatment may prevent further decline in his functioning (Birchwood et al, 1998) and consideration should be given to providing psychosocial (NHS Centre for Reviews & Dissemination, 2000) as well as pharmacological interventions. Compliance therapy (Kemp et al, 1998) has been shown to improve adherence to antipsychotic medication and survival times in the community. This may be of benefit to SR.

2. What are appropriate treatment doses of the commonly used antipsychotics?

Although therapeutic doses are more clearly defined for the newer antipsychotics, data for the older drugs do exist. Rifkin et al (1991) randomly assigned 87 new admissions with schizophrenia to receive 10, 30 or 80 mg of haloperidol daily and followed them over an eight-week period. The higher doses had no advantage over the 10 mg dose in either speed or magnitude of response. In a comprehensive review, Baldessarini et al (1988) concluded that daily doses of 500 mg chlorpromazine equivalents or above are always superior to placebo in psychosis trials, whereas 300 mg or less is only superior in two-thirds of trials. In addition, trials comparing high dose (mean dose 2649 mg chlorpromazine equivalents) with standard dose (mean dose 669 mg chlorpromazine equivalents) exhibit no difference in efficacy between the groups. McEvoy et al (1991) summarized that some patients respond to 100 mg chlorpromazine equivalents,

more to 200 mg and all who will by 500–700 mg. In line with this evidence, the licensed maximum daily dose for haloperidol has fallen from 120 mg daily to 15 mg daily (30 mg in treatment-resistant schizophrenia).

The optimum dose for risperidone is 4–8 mg per day with higher doses leading to an increased incidence of EPSEs (Chouinard et al, 1993) which negates the major advantage that risperidone holds over the older drugs. Risperidone is licensed up to a daily maximum dose of 16 mg and prescribers are more aware of this licensed maximum dose than the clinical efficacy data. Poor prescribing practice in this area was highlighted by a recent large survey of risperidone prescribing (Taylor et al, 1997) which found that only 15% of patients prescribed risperidone received it as the sole antipsychotic at a dose of 8 mg or less each day, without concurrent anticholinergics.

Olanzapine 10–20 mg daily and quetiapine 300–450 mg daily have also been shown to be therapeutic daily doses in the majority of patients.

High (above BNF maxima) doses of antipsychotics are probably of little benefit to the majority of patients who receive them, and are associated with significant risks. This area is reviewed in detail in the Royal College of Psychiatrists Consensus Statement on the use of high-dose antipsychotics (Thompson, 1994). This paper is essential reading for all practising psychiatrists.

Care should be taken not to confuse the non-specific sedation that many antipsychotics produce with actual antipsychotic effect. Sedation, if required early in treatment, should be provided by a sedative (usually a benzodiazepine, which can be withdrawn when no longer required) rather than as the side-effect of an antipsychotic.

3. What are the short- and long-term benefits of antipsychotics in schizophrenia? Quantify the risks of stopping treatment after recovery.

In the short term, antipsychotics control behaviour and improve the positive and negative symptoms of schizophrenia. There are some objective data to support improved outcomes with early intervention (Szymanski et al, 1996; Birtchwood et al, 1998), although this is controversial (Barnes et al, 2000). Sixty per cent of antipsychotic-treated patients (as

compared with 20% who receive placebo) have been shown to improve significantly over a six-week period (American Psychiatric Association, 1997). Although a significant part of the therapeutic benefit occurs in this time span (Keck et al, 1989), improvements in socialization can continue for many months.

Many double-blind, placebo-controlled trials have demonstrated the benefits of antipsychotics in the maintenance phase of schizophrenia. In a summary of data involving 3609 patients, 20% of those who were maintained on active medication relapsed as compared with 53% of those who were maintained on placebo (Kaplin and Sadcock, 1989). In a review of 66 studies on antipsychotic withdrawal involving 4365 patients who were followed up for a mean of 9.7 months, over three times as many patients withdrawn from antipsychotics (53%) relapsed compared to those who remained on maintenance treatment (16%) (Gilbert et al, 1995). The many studies that are reviewed in this paper lead to the conclusion that the shorter the symptom-free period and the longer the duration of follow-up, the more likely is relapse.

Relapse has been shown to be more likely after abrupt rather than gradual discontinuation of oral antipsychotics (Viguera et al, 1997), with depot antipsychotics offering a similar protective effect, probably due to the slow elimination of active drug from the body.

Evidence from primary research, as well as from consensus opinions of expert groups (Kissling et al, 1991), indicates that first-episode patients should be treated with antipsychotics for at least one to two years and multi-episode patients for at least five years.

The patient in this case has had two episodes of illness in a 14-month period. Relapse followed five months after his depot was stopped. He is at high risk of further episodes if he does not comply with maintenance antipsychotic treatment.

4. What are the short- and long-term risks of anticholinergics?

Anticholinergics can cause dry mouth, blurred vision, constipation, urinary retention and tachycardia. Higher doses can cause confusion, particularly in the elderly. Some patients feel subjectively better when taking anticholinergics and, in a minority, they are misused for their euphoric effects.

Anticholinergics worsen existing tardive dyskinesia (TD) (Greil et al, 1985), but there is little objective evidence to support anticholinergics as an independent risk factor for TD (Gardos and Cole, 1983). Anticholinergics are more likely to be prescribed for those patients who experience EPSEs early in treatment, a group who are known to be more likely to develop TD. It has been suggested that the use of anticholinergics in these patients is coincidental to the development of TD, rather than being directly responsible (a so-called epiphenomenon) (Barnes, 1990).

Key points

- The more rapidly psychosis is treated, the more favourable the long-term outcome may be.
- Non-specific sedation should not be confused with antipsychotic effect.
- There is good evidence to suggest that the doses of antipsychotics routinely used in clinical practice are too high.
- Atypical antipsychotics are associated with fewer EPSEs but more weight gain. They are much more expensive.
- The clinical benefits of atypicals can only be realized if they are used as antipsychotic monotherapy.
- Individual antipsychotics have different side-effect profiles - prescribers should be aware of these differences.
- The 'best-fit' antipsychotic should be found for each patient.
- Patients should be afforded the opportunity to express their own preferences of drug choice.
- First-episode patients should be treated for one to two years, multi-episode patients for at least five years.
- Relapse is less likely after discontinuation of depot or slow reduction of oral therapy, than after abrupt withdrawal of oral antipsychotics.
- The relapse rate within one to two years is three times higher in those who stop treatment compared with those who continue to take antipsychotics.

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3

Refractory schizophrenia

David Taylor

SK is a 26-year-old Iranian man with a five-year history of psychotic illness. His first episode was treated in Iran with trifluoperazine, prochlorperazine and sulpiride in combination. Clinical details are scant, but it appears that he recovered well and was discharged from hospital after three weeks.

SK later came to the UK and was soon admitted with marked delusions, auditory hallucinations and thought disorder with neologisms. He responded to chlorpromazine 600 mg daily and was discharged. A diagnosis of paranoid schizophrenia was made.

More recently, SK was referred to a specialist psychosis unit following poor recent response to a range of antipsychotics (trifluoperazine 60 mg daily; haloperidol 40 mg daily; zuclopenthixol depot 600 mg weekly). He admitted to hearing voices telling him to 'smoke' (he chain-smokes 50+ cigarettes a day) and to 'hit-out', and was profoundly suspicious of other

patients. SK appeared lethargic with no arm swinging on walking and a slow monotone voice. His medication on referral was as follows:

Risperidone	*3 mg bd*
Carbamazepine	*300 mg bd*
Clonazepam	*2 mg on*
Thioridazine	*100 mg at night*

Questions

1. What is the drug of choice in this patient?
2. What is the evidence supporting the use of new atypical antipsychotics in refractory schizophrenia?
3. How is clozapine therapy optimized?
4. How are adverse effects managed?

Answers

1. What is the drug of choice in this patient?

SK is evidently suffering from schizophrenia which is refractory to treatment. Clozapine is the only drug shown unequivocally to be effective in refractory schizophrenia and it is therefore the drug of choice in SK.

Evidence of the efficacy of clozapine in refractory schizophrenia derives largely from the seminal study of Kane et al (1988). Subjects in this study were defined as treatment resistant: each had received at least three antipsychotics at high dose for six weeks and had not responded. All were severely ill with a Brief Psychiatric Rating Scale (BPRS) (scored 1–7) score of at least 45. In a single-blind run-in period, all subjects received high-dose haloperidol to ensure treatment resistance (1.6% of subjects responded). Subjects then received either clozapine (up to 900 mg daily) or chlorpromazine (up to 1800 mg daily). After six weeks, 30% of clozapine-treated patients had responded (>20% fall in BPRS and final score of <35) compared with 4% of the chlorpromazine-treated group.

Other studies have shown that response rates with clozapine are higher than 60% if the drug is given for

up to a year (Meltzer et al, 1989; Conley et al, 1997). All patients should therefore receive at least a six-month trial of clozapine to assess its effectiveness properly.

In the case of SK, clozapine should be introduced as early as possible. Carbamazepine should be withdrawn gradually before clozapine is started. Assuming a normal full blood count, risperidone and thioridazine may be slowly withdrawn once clozapine has been initiated (Taylor, 1997a), although risperidone can increase clozapine plasma levels (Taylor, 1997b). It should be noted that SK is a heavy smoker. Cigarette smoke induces the hepatic metabolizing enzyme CPY1A2, which is involved in the metabolism of clozapine (Taylor, 1997b). SK may, therefore, eventually require a higher than average dose of clozapine.

2. What is the evidence supporting the use of new atypical antipsychotics in refractory schizophrenia?

Evidence relating to the use of atypical drugs other than clozapine in refractory schizophrenia is weak and often inconsistent. Some manufacturer-sponsored studies appear to suggest important efficacy in resistant illness. For example, risperidone (Bondolfi et al, 1998) and olanzapine (Beasley et al, 1999) have both been compared with clozapine in randomized controlled trials and been suggested to have equal efficacy in resistant schizophrenia. Zotepine has also apparently been effectively used in refractory psychoses (Harada et al, 1987; Prakash and Lamb, 1998) and quetiapine seems to be effective in those showing only partial response to previous antipsychotic therapy (Emsley et al, 2000). Nevertheless, a greater body of evidence, not to mention widespread clinical experience, suggests that atypical antipsychotics have very limited utility in refractory psychosis.

The most comprehensive systematic review conducted so far (Taylor and Duncan-McConnell, 2000) concludes that only clozapine has sufficient supporting evidence to recommend its use in refractory illness. Other drugs are condemned on the basis of the laxity of definition of treatment resistance in 'positive' trials and on the negative findings of trials with more rigidly defined treatment resistance (eg Conley et al, 1999) and of clozapine-switching studies (eg Lacy et al, 1995). It should also be noted that clozapine

is effective where other atypicals have failed (Conley et al, 1999).

Overall, there is little to support the use of non-clozapine atypical antipsychotics in true treatment-refractory schizophrenia. Clozapine remains the treatment of choice, despite the difficulties inherent in its use (Reus, 1997; Emsley, 2000; Taylor and Duncan-McConnell, 2000).

3. How is clozapine therapy optimized?

Clozapine is introduced at 12.5 mg at night and the dose increased over two to three weeks. For most patients a dose of 400 mg daily is aimed for, at least initially. Further increases up to a maximum of 900 mg daily may be necessary. It is common to use increments of 50 mg daily perhaps every one or two weeks, adjusted according to careful evaluation. Recognized clinical rating scales such as the BPRS and the Clinical Global Impression are helpful in measuring change and provide a useful, meaningful record of drug response.

Many centres use plasma level monitoring to optimize clozapine dose. Plasma levels >350 μg/l are usually associated with response (Taylor and Duncan, 1995), although this threshold level should be considered simply as a guide: many patients respond with lower levels and some fail to respond despite higher levels. Plasma level determinations are also invaluable in revealing occult non-compliance; a rare but significant problem even with inpatients. They can also help identify patients with high clearance rates and subtherapeutic levels (usually male smokers). Dangerous pharmacokinetic interactions (Taylor, 1997b) can also be identified and closely monitored.

Once dose and plasma level have been optimized, clozapine should be given for a lengthy period to evaluate response. How long this evaluation period should be is the subject of some debate. Meltzer et al (1989) showed that clinical response to clozapine was delayed in many patients, with some not reaching a predetermined threshold for response for six or nine months. A year-long trial period thus became standard with clinicians noting continued improvement even beyond this time. However, this practice has been challenged (Carpenter et al, 1995) on the basis that patients do not suddenly begin to improve after many months but do so gradually (but noticeably), reaching a somewhat arbitrary threshold for response after

many months. An assessment period of two to four months was suggested, with patients showing 'little or no benefit' during this time being recommended for withdrawal. This view, in turn, was robustly challenged (Meltzer, 1995) and so the debate has continued. More recently Conley et al (1997) have contributed to this debate with the observation that all responders meet response criteria within eight weeks of a change in dose. Thus, there seems little point in continuing with a given dose of clozapine beyond this time. It was also noted that dose titration to 600 mg daily over 12–18 weeks identified 90% of responders. Plasma level monitoring was not used.

Taken together, these observations and arguments provide clinicians with little in the way of clear, practical guidance. Perhaps the best that can be concluded is as follows:

- Begin clozapine and slowly increase to 400 mg daily over two to three weeks, or longer if necessary.
- If no response is observed over several weeks at 400 mg daily, then the dose should be adjusted to afford a plasma level >350 μg/l.
- If no response is observed (again over several weeks), the dose should be increased to the maximum tolerated dose.
- If no response is observed after eight weeks at the maximum tolerated dose, then clozapine augmentation strategies may be considered.

In practice, these guidelines will usually result in trial periods of four to six months overall. Predetermined criteria for response should be drawn up locally. A 20% fall in BPRS score is a widely accepted criterion for useful clinical improvement, but overall quality of life is also an important consideration. The co-administration of other antipsychotics should be avoided. A possible exception to this is low-dose sulpiride, which may be effective in clozapine partial responders (Shiloh et al, 1997). However, this trial should be interpreted with caution, as the cohorts randomized to receive clozapine and placebo had significantly different baseline scores on some items, indicating that they may have been a more chronically ill group than those randomized to receive clozapine and sulpiride. Also, patient numbers were low. Other augmentation strategies such as benzodiazepines, lithium, valproate and lamotrigine have been investigated (Chong and Remington 2000; Taylor et

al, 2001) and may be helpful in some patients.

4. How are adverse effects managed?
The most serious adverse effects of clozapine are neutropenia and agranulocytosis, which are well managed by the Clozaril Patient Monitoring Service run by Novartis (Atkin et al, 1996). These potentially fatal adverse effects should be considered the only adverse effects serious enough to warrant discontinuation of clozapine. All other adverse effects eventually abate or can be successfully managed with remedial therapies.

Drowsiness can be severe but this wears off after three to six months at the most. Giving a larger proportion of the total daily dose at night often helps. **Constipation** is common but responds to stimulant (eg senna) and bulk forming (eg ispaghula) laxatives in combination. **Hypersalivation** is also common but may be effectively treated by hyoscine 300–600 μg at night or pirenzepine 25–100 mg daily (Fritze and Elliger, 1995). **Hypotension** is usually relieved by reducing the dose of clozapine or slowing the rate of increase. In severe, dose-limiting, cases moclobemide in combination with Bovril is helpful (Taylor et al, 1995). **Hypertension** occurs less often and can be successfully treated with propranolol (George and Winther, 1996).

Weight gain is very common (Bustillo et al, 1996) and difficult to prevent or treat. Dietary counselling would seem a sensible precaution but there are no firm data on its effectiveness.

Nocturnal enuresis is rare but often troublesome when it does occur. Avoiding late evening fluids is helpful and desmopressin can be used in severe cases (Aponowitz et al, 1995).

Seizures occur at high doses (Wilson and Claussen, 1994) but are effectively prevented by co-administration of therapeutic doses (plasma levels 50–100 mg/l) of valproate. Problems related to **impaired glucose tolerance** may also occur (Mir and Taylor, 2001).

Nausea is quite common but generally short-lived.

Clozapine has also been associated with **hypersensitivity myocarditis** and **cardiomyopathy** (Killian et al, 1999). In common with other

antipsychotic drugs, it may also increase the risk of **thromboembolism** (Zornberg and Jick, 2000). These effects are rare. See Chapter 4 for a full discussion of the adverse effects of clozapine.

Key points

- Clozapine is the drug of choice for treatment refractory schizophrenia.
- There is no good objective evidence demonstrating the efficacy of other atypical antipsychotics in treatment-refractory schizophrenia.
- Serum-level monitoring may be useful in optimizing clozapine treatment, aiming for levels >350 μg/l.
- If no response is shown to the maximum tolerated dose administered for eight weeks, clozapine should be withdrawn.
- Agranulocytosis is the most serious side-effect of clozapine. This risk is managed safely by the CPMS.
- Drowsiness, constipation, hypersalivation, nocturnal enuresis and seizures can all occur, but can be managed. Symptomatic postural hypotension and weight gain are more difficult to manage.

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4

Managing adverse effects of clozapine

Shubhra Mace

RJ, a 22-year-old man with a long history of schizophrenia, is admitted to hospital under Section 3 of the Mental Health Act, after relapsing in the community. He is not taking any medication when admitted but has in the past been prescribed several different antipsychotics, both alone and in combination. Medical records show that he had only partially responded to these strategies.

Once in hospital RJ is prescribed clozapine. Three weeks later, at a dose of 300 mg nocte, he is found to be wetting the bed at night. On routine examination it is also noted that his blood pressure was 140/105 mmHg. A diagnosis of hypertension is made and an antihypertensive drug prescribed.

Over the following six weeks the dose of clozapine is gradually increased and it is suggested that sodium valproate be added to his existing therapy.

Questions

1. Is urinary incontinence likely to be caused by clozapine? What are the treatment options?
2. How is clozapine-induced hypertension best managed?
3. Why might valproate be prescribed with clozapine?

Answers

1. Is urinary incontinence likely to be caused by clozapine? What are the treatment options?

Yes. Urinary incontinence (UI) is a recognized side-effect of clozapine with estimates of its prevalence ranging from 0.23% (Lieberman, 1998) to 27% (Centorino et al, 1994). It is an embarrassing side-effect and as such is likely to be underreported by patients.

The mechanism of clozapine-induced UI remains unclear. Several mechanisms have been proposed and a number of management options have been tried. Suggested mechanisms include α-adrenergic blockade, H_1 blockade (precipitating deep sleep), cholinergic blockade (precipitating urinary retention with overflow) and nocturnal seizures. In a series of case reports (Steingard, 1994; Aponowitz, 1995; Frankenburg et al, 1996) the authors described the use of desmopressin to manage UI caused by clozapine. Desmopressin, a synthetic analogue of antidiuretic hormone, was administered (10 μg) into each nostril at night providing complete resolution of symptoms

Two anticholinergic agents, oxybutinin and trihexyphenidyl (benzhexol) have also been investigated in the treatment of UI. Trihexyphenidyl (benzhexol) 5 mg at night appeared to reverse the symptoms of enuresis in two patients (Poyurovsky et al, 1996). In a different group of five patients, oxybutinin 5–15 mg a day seemed to reduce bladder urgency (Frankenburg et al, 1996). Ephedrine has been tested in a small open trial (n = 16) by Fuller et al (1996). UI resolved completely in 12 out of the 16 patients treated with

ephedrine 25–150 mg a day. Verapamil, a calcium-channel blocker, was reported to treat enuretic activity successfully in a single case report (Pojurovsky, 1995): doses of between 40 and 80 mg daily were used. When verapamil was replaced with placebo, enuretic activity increased, which then disappeared on reinstating the verapamil (Pojurovsky et al, 1995). In contrast, Grinshpoon et al (1994) found verapamil to have no effect on enuresis in 11 drug-free healthy adults.

Despite being markedly anticholinergic, clozapine also exhibits some cholinomimetic activity that may lead to UI, and this may explain the observed efficacy of anticholinergic agents. Two mechanisms for the efficacy of ephedrine in clozapine-induced UI have been proposed. One explanation is that the activating effects of ephedrine counteract the sedation caused by clozapine. A second explanation is that ephedrine stimulates α- and β-adrenergic receptors, thus relaxing the bladder smooth muscle and preventing UI (Fuller et al, 1996). Reasons for the efficacy of verapamil in clozapine-induced UI remain unclear.

It is advisable that, wherever possible, non-drug interventions should be considered to treat UI, for example dose manipulation to prevent peak clozapine levels at night and the avoidance of large volumes of fluid before bedtime.

It is interesting to note that clozapine has itself been shown to treat UI in a patient who remained incontinent whilst on trifluoperazine and subsequently sulpiride (Mathew et al, 1996). On switching to clozapine, the frequency of wetting decreased as the dose of clozapine was increased. No further episodes of UI were seen once a dose of 400 mg of clozapine was reached.

2. How is clozapine-induced hypertension best managed?

Hypotension occurs commonly with clozapine and is caused by antagonism of α_1-adrenergic receptors. Hypertension, which is seen less often, may be a result of presynaptic α_2-adrenergic blockade, (antagonism of negative feedback).

High clozapine plasma levels may be a contributory factor in hypertension, as suggested by Sloan and Boyle (1997). However, other case reports (Gupta, 1994; George and Winther, 1996; Shiwach, 1998) indicate the emergence of hypertension at seemingly subtherapeutic doses of clozapine,

although the authors failed to give details of the plasma levels.

Most of the published case reports of the treatment of clozapine-induced hypertension include an account of the efficacy of β-blockers. Propranolol, atenolol and pindolol have all successfully reversed clozapine-induced hypertension (Gupta, 1994; Sloan and Boyle, 1997; George and Winther, 1996; Schiwach, 1998). George and Winther (1996) used propranolol 180 mg daily and found that this allowed for the dose of clozapine to be increased without a significant increase in blood pressure. Atenolol 50 mg daily was used to treat hypertension in another of the cases (Gupta, 1994). A normal blood pressure reading was achieved within five days. At six month follow-up the patient had achieved a target clozapine dose whilst remaining on the same dose of atenolol. In the third case (Shiwach, 1998) the author used pindolol 5 mg twice daily to treat clozapine-induced hypertension, after an unsuccessful trial of nifedipine. The blood pressure readings were normalized within two days of starting pindolol; however, clozapine was discontinued in this patient before a therapeutic dose was achieved and so it is difficult to assess the full efficacy of pindolol.

Clozapine has been associated with elevated catecholamines along with hypertension, similar to the presentation of phaeochromocytoma (Li et al, 1997). It is important to distinguish between these two conditions. In the case of the clozapine-induced condition, urinary catecholamines and blood pressure return to a normal level once the drug is withdrawn. Clearly, in phaeochromocytoma, blood pressure does not normalize.

If possible, a slower dose titration or a dose reduction should be the first option in the management of clozapine-induced hypertension. Alternatively, a β-blocker such as propranolol or atenolol may be the drug treatment of choice.

As well as hypo- and hypertension, clozapine is associated with other adverse cardiac effects. These include tachycardia, various ECG abnormalities (Kang et al, 2000), myocarditis and cardiomyopathy (Killian et al, 1999). Any patient who experiences hypertension as a side-effect of clozapine should have an ECG and full clinical examination to rule out any other significant cardiac pathology. Indeed, regular ECGs are a

sensible precaution in all patients on clozapine.

3. Why might valproate be prescribed with clozapine?

Sodium valproate is an anticonvulsant drug that also has mood-stabilizing properties. It has been used to augment the effect of antipsychotic drugs in treatment-refractory illnesses, especially where mood disturbance is apparent. In patients on clozapine, valproate may be used for either reason, or sometimes both.

Clozapine has been reported to cause electroencephalogram (EEG) changes, myoclonic jerks and seizures (Devinsky et al, 1991; Gouzoulis et al, 1991; Berman et al, 1992; Gouzoulis et al, 1993; Gunther et al, 1993; Antelo et al, 1994; Malow et al, 1994; Meltzer and Ranjan, 1994; Pacia and Devinsky, 1994; Welch et al, 1994; Barak et al, 1996; Sajatovic and Meltzer, 1996). The true incidence is unclear. However, it appears that the risk of a seizure with clozapine increases with increased doses (plasma concentrations) (Pacia and Devinsky, 1994) and is greatest with doses of 600 mg daily or greater. In support of this is the observation that in a retrospective study (Fleischhaker et al, 1994) comparing clozapine doses used in European trials with those used in American trials, the authors found that in the higher dosed American trials, seizures were more prevalent. Seizures may also occur during dosage titration when clozapine is initiated, particularly if the dose is increased rapidly. RJ experiences UI. Nocturnal seizures are one potential cause.

Various anticonvulsant medications have been tried in the treatment and prophylaxis of clozapine-induced seizures. The majority of the data relate to phenytoin, phenobarbitone, clonazepam, carbamazepine and valproate. There are no data comparing the different anticonvulsant medications.

Overall, there seems to be a reasonable agreement on the guidelines for the management of clozapine-related seizures. Carbamazepine (Devinsky and Pacia, 1994; Toth and Frankenburg, 1994) and phenytoin (Toth and Frankenburg, 1994) can both cause blood dyscrasias (neutropenia and agranulocytosis) which precludes their use. Valproate may be the anticonvulsant of choice in clozapine-induced seizures. It appears to be well tolerated in practice and the

combination of valproate and clozapine is safe and effective (Kando et al, 1994; Taner et al, 1998). It is important, however, to be aware of additive adverse effects of valproate and clozapine, namely weight gain and sedation. For the treatment of myoclonic jerking, clonazepam may also be considered.

Wherever possible non-drug measures should be considered. These include dose reduction or dose manipulation to avoid high peaks of clozapine. In the event of a seizure, clozapine should be omitted for 24 hours, then restarted at 50% of the previous dose. Clozapine plasma levels should be monitored and the dose increased cautiously as appropriate. In practice, valproate is the most widely used anticonvulsant for the treatment or prophylaxis of clozapine-induced seizures. The adult starting dose is 500 mg daily of the modified release preparation. The dose (usually 1000–2000 mg daily) should then be adjusted to achieve a plasma level of 50–100 mg/l. Patients who are at a high risk of having a seizure, e.g. those with a history of epilepsy or patients with a head injury, should be prescribed valproate prophylactically before clozapine is initiated.

Sodium valproate is also an effective mood-stabilizing drug (see Chapter 23) and has been used as an augmentation strategy when clozapine alone is only partially effective (Chong and Remington, 2000). It may have been prescribed for RJ for either of these indications.

Key points

- Hypertension is an uncommon but established side-effect of clozapine. It may be dose related.
- Seizures and UI are dose related, although seizures may also occur with rapid dosage titration.
- Wherever possible, dose manipulation should be the first option in the management of UI, hypertension and seizures.
- If dose adjustment or reduction is not possible, hypertension can be treated with β-blockers, seizures with valproate and UI with anticholinergics or desmopressin.

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5

Negative symptoms

Carol Paton

PF, a 21-year-old man, was visited in a mental health aftercare hostel by his community psychiatric nurse (CPN) in order to administer his depot injection (fluphenazine decanoat 100 mg every two weeks). His keyworker reported increasing problems with PF's self-care and motivation. It was increasingly difficult to persuade him to have a bath and he had not attended the day centre for several weeks. PF isolated himself in his room where he spent most of his time smoking in bed. The floor was covered in cigarette burns and staff were concerned about possible fire risk.

PF had been admitted to hospital briefly, aged 17, when he described derealization and depersonalization and some passivity phenomena. PF was known to be abusing cannabis heavily at this time and a diagnosis of drug-induced psychosis was made. He received haloperidol 20 mg bd for three weeks in hospital, but discharged himself against medical advice and

never attended outpatients or his GP for further supplies. PF was again admitted, aged 20, 'in a much deteriorated state' suffering from third-person auditory hallucinations, thought disorder, and delusions about electrical equipment. These symptoms responded well to fluphenazine 100 mg every two weeks, but significant problems with self-care, motivation and social skills remained.

PF is the only child of a single mother, was a forceps delivery and was slow to achieve milestones (walking age two, talking age two and a half). Physical examination noted an underweight young man with a squint in his left eye. He had marked psychomotor slowing, lack of facial expression and a resting tremor. Routine blood tests were normal. Urine drug screen was negative.

Questions

1. Which pharmacological interventions would be appropriate?
2. Are traditional antipsychotics effective against primary negative symptoms?
3. Are atypical antipsychotics effective against primary negative symptoms?
4. Can any efficacy against primary negative symptoms in the acute phase of illness be generalized to patients with enduring negative symptoms?

Answers

1. Which pharmacological interventions would be appropriate?

This patient's positive symptoms have responded well to fluphenazine depot and negative symptoms currently dominate the clinical picture. Negative symptoms of schizophrenia include: alogia (poverty of speech/content), flattened/blunted affect, anhedonia, asociality, avolition/apathy and motor retardation. Subjective sadness, pessimism and suicidal intent are not considered to be negative symptoms (Coffey, 1994). Negative symptoms are generally considered to be more biological in nature than positive symptoms and there are both organic and dynamic hypotheses. Negative symptoms have been associated with enlarged cerebral ventricles, intellectual

impairment, lack of response to antipsychotics and poor prognosis (Crow, 1980), and have been said to predict poor functioning in both the short and the long term (Pogue-Geile and Harrow, 1985). A biological aetiology for enduring negative symptoms (deficit state) is supported by EEG changes which are consistent with a hypofrontality hypothesis. More severe negative symptoms and an earlier age of onset are associated with low interleukin-2 production which may reflect an autoimmune disturbance (reviewed by McPhillips and Barnes, 1997).

Negative symptoms may have many origins and it is important to determine the most likely cause in any individual case before embarking on a treatment regimen. Carpenter (1996), describes negative symptoms as being either primary (transient or enduring), or secondary to positive symptoms (eg asociality secondary to paranoia), bradykinesia [extrapyramidal side-effects (EPSEs): lack of emotional spontaneity, retarded speech, few gestures, decreased movements], depression (eg anhedonia, social withdrawal, apathy) or institutionalization. Primary transient negative symptoms must be differentiated from both primary enduring negative symptoms (deficit state) and secondary negative symptoms caused by antipsychotic side-effects. This is not a simple task, as these symptoms are not mutually exclusive.

The patient in this case has made a good response to fluphenazine with respect to positive symptoms. The negative symptoms that remain may be primary enduring negative symptoms, secondary to EPSEs or depression, or to any combination of these factors. The long-standing problem that PF has had with lack of motivation is likely to be a primary negative symptom, whereas the psychomotor slowing, lack of facial expression and resting tremor are probably medication induced (Kelley et al, 1999).

The dose of depot prescribed for PF is quite high and a reasonable first step would be to reduce this. Antipsychotic dosage reduction studies which have observed patients on long-term treatment through periods of dosage reduction have noted improvements in blunted affect, emotional withdrawal and psychomotor retardation (Marder et al, 1984). Improvements are slow to

emerge, particularly with depot treatment. A trial of an anticholinergic, with the aim of reducing EPSEs, may also be worthwhile, as may a trial of an atypical antipsychotic (see question 3). Depending on further evaluation of the mental state, treatment with an antidepressant may be appropriate.

2. Are traditional antipsychotics effective against primary negative symptoms?

Clinical trials which demonstrate the efficacy of the older typical antipsychotics routinely show a broad-spectrum effect against both positive and negative symptoms in the acute phase. Negative symptoms are perhaps less likely to respond in the maintenance phase when positive symptoms are effectively in remission. Early studies found that indifference to the environment, apathy, inappropriate affect, poor social participation and poor self-care responded to antipsychotic treatment, whereas these symptoms developed over time in placebo-treated patients (Goldberg et al, 1965). Waddington et al (1995) found that in a cohort of older patients with schizophrenia, an increased period of initial untreated psychosis led to a later increased incidence of poverty of speech. The earlier the antipsychotic treatment was started in this group, the less the decline over time.

These findings would be consistent with the hypotheses that:

- Primary negative symptoms may be secondary to positive symptoms, e.g. where social withdrawal is a result of acute paranoid delusions (Carpenter, 1996).
- The earlier treatment with antipsychotics is started, the better the long-term outcome (Wyatt, 1995). Early effective treatment with antipsychotics may alter the trajectory of decline and prevent the development of enduring negative symptoms.

In conclusion, while conventional antipsychotics may treat negative symptoms that are secondary to acute positive symptoms, or decrease relapse rates and prevent the development of chronic symptoms, there is no evidence to show that they have significant efficacy against primary enduring negative symptoms. This is complicated by the fact that conventional antipsychotics may cause so-called secondary negative symptoms (due to EPSEs).

3. Are atypical antipsychotics effective against primary negative symptoms?

Atypical antipsychotics are so named because they have at least equivalent antipsychotic potency to the older compounds but with significantly less potential for producing EPSEs. This may be due to their relative selectivity for mesolimbic dopamine pathways or their high 5HT2:D2 blocking ratio or both. In clinical practice, most atypicals also show slightly superior efficacy to typicals in the treatment of positive symptoms and this may translate into improved social integration. Clozapine is uniquely effective in treatment-resistant illness. Risperidone, olanzapine, quetiapine, amisulpride, zotepine and clozapine would therefore be expected to treat positive symptoms without producing secondary negative symptoms. Whether atypicals have efficacy against negative symptoms beyond the secondary improvements from reduced positive symptoms and the relative lack of EPSEs is the subject of some debate.

It has been postulated that serotonergic antagonism would counteract negative symptoms that may arise from hypodopaminergic functioning in prefrontal cortical areas. Initial hope that potent 5HT2 blockade might be beneficial in the treatment of negative symptoms came from a study by Duinkerke et al (1993), in which ritanserin, a selective 5HT2 and 5HT1C antagonist, was added to stable treatment regimes with typical antipsychotics. Facial expression, flattened affect and relationships with friends and peers were all noted to improve.

Sertindole (currently unavailable due to concerns over QTc prolongation) is an atypical antipsychotic which is relatively selective for mesolimbic D2 pathways, has a high 5HT2:D2 blocking ratio and has an incidence of EPSEs indistinguishable from those of placebo. In an efficacy trial (patients were not specifically selected for the presence of negative symptoms) which randomized 497 patients to receive sertindole 12, 20 or 24 mg, haloperidol 8 or 16 mg, or placebo for eight weeks, EPSEs occurred no more frequently with sertindole than with placebo. Using the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1983), no dose of sertindole was more effective than any dose of haloperidol and only sertindole 20 mg was significantly more effective than placebo for negative symptoms (Zimbroff et al, 1997).

A meta-analysis of risperidone studies (Carman et al, 1995), which used the Positive and Negative Syndrome Scale (PANSS: Kay et al, 1987) and SANS scores to determine the severity of negative symptoms before and after risperidone treatment, concluded that patients were 1.5 times more likely to experience clinically significant reductions in negative symptoms with risperidone than with placebo. Risperidone was said to have an equal effect directly on primary negative symptoms, and indirectly through decreasing positive symptoms and EPSEs or depression. The results of this meta-analysis were probably influenced by the publication bias that operates in favour of positive findings when small patient numbers are included in trials. The largest study included in this meta-analysis was that of Peuskens et al (1995), where 450 patients received 4 or 8 mg risperidone and 222 patients received 10 mg haloperidol for eight weeks. There was no difference between treatment groups in the response of primary negative symptoms in this trial ($p = 0.39$).

In a trial of olanzapine efficacy, 335 patients (90% of whom had a chronic course with an acute exacerbation) were randomized to receive a low (mean 5 mg), medium (mean 10 mg) or high (mean 15 mg) dose of olanzapine, haloperidol or placebo (Tollefson et al, 1997). One hundred and thirty-nine patients completed the six-week trial and the data were analysed by 'intent to treat' analysis. A complex statistical model was used to separate negative symptoms due to illness from those due to side-effects. The later the age at onset of illness, the greater the response of negative symptoms in this trial. There was a positive relationship between improvements in negative symptoms and improvements in mood and EPSEs. The authors concluded that olanzapine was more effective than haloperidol in both primary and secondary (drug-induced) negative symptoms. It has been suggested that the statistical model used in this study is not valid, as primary and secondary negative symptoms may be independent conceptually but they have not been proven to be statistically independent (Kelley et al, 1999).

There are no published data for quetiapine demonstrating efficacy against negative symptoms superior to that shown by traditional antipsychotics.

Clozapine is uniquely effective in patients with treatment-resistant schizophrenia and the large study by Kane et al (1988) demonstrated superior efficacy to chlorpromazine for both positive and negative symptoms. The very significant response of positive symptoms and lack of EPSEs could explain the improvement in negative symptoms in this study. A further randomized double-blind study by Rosenheck et al (1999) found clozapine to be significantly more effective than haloperidol overall, but to have no independent effect on negative symptoms after the improvement in positive symptoms had been controlled for.

A further small study compared the efficacy and side-effect profiles of clozapine and risperidone (Breier et al, 1999). Clozapine produced greater improvements in positive symptoms and was associated with fewer EPSEs than risperidone. There was no difference between the treatments on any measure of negative symptoms.

4. Can any efficacy against primary negative symptoms in the acute phase of illness be generalized to patients with enduring negative symptoms?

Patients who have two or more moderately severe primary negative symptoms that are stable over the course of at least one year are said to have trait negative symptoms or the deficit state.

Amisulpride is an antipsychotic that has high affinity for D2 and D3 receptors. At low doses it blocks the presynaptic D3 autoreceptor, thus facilitating dopamine transmission, while at higher doses it blocks postsynaptic D2 receptors in the same manner as conventional antipsychotics. In a double-blind, placebo-controlled trial of 104 patients (who had negative symptoms for a mean of eight years) randomized to receive amisulpride 100 mg, 300 mg or placebo for six weeks (Boyer et al, 1995), there was no change in positive symptoms or EPSEs across the three treatment groups, while both doses of active drug were significantly more effective than placebo against negative symptoms using ratings on SANS. Significant improvements in affective blunting, alogia, avolition/apathy and attentional impairment were seen in up to 50% of the amisulpride-treated patients compared with up to 25% of the placebo-treated patients. There was a pretreatment washout phase of six weeks to exclude improvements in

secondary negative symptoms. These results are supported by a further randomized double-blind placebo-controlled trial in which 141 patients were treated with amisulpride 100 mg or placebo for six weeks (Loo et al, 1997). Patients were selected on the grounds of having a chronic illness with residual negative symptoms. Improvement was defined as a 50% reduction in baseline SANS score. Forty-two per cent of amisulpride patients improved compared with 15.5% of placebo patients. Again, significant improvements were seen in affective flattening, alogia, avolition/apathy, anhedonia/asociality and attentional impairment, and these were not correlated with improvements in positive symptoms or EPSEs.

Superior efficacy over placebo in this patient group has not translated into superior efficacy over haloperidol. Amisulpride has been compared with low-dose haloperidol in 60 patients with predominant enduring negative symptoms in a randomized double-blind trial (Speller et al, 1997). This study followed patients over a period of one year while attempts at dosage reduction were made. The majority of patients randomized to amisulpride received a dose of 150 mg daily or less at the end of the trial period, while the majority of the haloperidol group received 4.5 mg daily or less. The effect of either treatment on negative symptoms was modest and, although the amisulpride group fared slightly better, the difference did not reach statistical significance. The power of this study was low.

In a 12-month open-label trial of 50 treatment-resistant patients, clozapine was found to have a significant antipsychotic effect in both deficit and non-deficit patients (Conley et al, 1994). Improvement in negative symptoms was observed only in the non-deficit group. In a further double-blind efficacy trial of clozapine (Brier et al, 1994), in which 39 stable outpatients who were partial responders to previous antipsychotic regimens were randomized to receive 200–600 mg clozapine or 10–30 mg haloperidol daily for 10 weeks, clozapine was found to be significantly more effective than haloperidol in the treatment of both positive and negative symptoms. On further analysis, the significant difference in efficacy against negative symptoms was found to be due to a modest decrease in the clozapine group combined with a modest increase in the haloperidol

group. In the subgroup of patients in this trial who fulfilled the criteria for the deficit syndrome (n = 11), clozapine and haloperidol were equally effective against negative symptoms.

In a small open-label study of olanzapine in patients with severe negative symptoms, those who had non-deficit symptoms demonstrated improvements in both positive and negative symptoms, whereas those with deficit symptoms showed improvements in EPSEs (secondary negative symptoms) only (Kopelowicza et al, 2000).

In conclusion, there is no robust data to support the superior efficacy of any antipsychotic in the treatment of enduring primary negative symptoms. Maximum benefit is obtained with low-dose antipsychotics. This therapeutic effect is modest at best.

Key points

- Negative symptoms can be primary (transient or enduring) or secondary to positive symptoms, depression, EPSEs or institutionalization. Intervention is dependent upon aetiology.
- The earlier antipsychotic treatment is started, the less likely the patient may be to subsequently develop negative symptoms.
- Traditional antipsychotics have limited efficacy against negative symptoms and can cause secondary negative symptoms (through their propensity to cause EPSEs).
- Atypical antipsychotics are less likely to cause EPSEs and, therefore, secondary negative symptoms than the older drugs, but are not convincingly more effective against primary negative symptoms.
- Clozapine is uniquely effective against resistant positive symptoms and is virtually devoid of EPSEs, properties which translate clinically into a very low incidence of secondary negative symptoms. It is not convincingly effective against primary enduring negative symptoms ('deficit state').

- There are no robust data to support any antipsychotic having more than a very modest effect in the treatment of primary enduring negative symptoms.

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6

Treatment of psychosis in people with epilepsy

Denise McConnell

RT, a 28-year-old Caucasian man with a 14-year history of refractory complex-partial seizures was brought to hospital by the police. He had threatened his mother with a knife because he believed she was collaborating with aliens to poison him. Mental state examination revealed auditory hallucinations, thought insertion and thought blocking, delusions of persecution and loosening of associations. He was admitted to hospital and prescribed chlorpromazine 250 mg four times a day. He was later diagnosed as having a schizophrenia-like psychosis of epilepsy.

Medications on admission:

Vigabatrin	2000 mg bd (for last six months)
Valproate	500 mg bd (10 years)
Carbamazepine	200 mg bd (one year)

Over the following month it was noted that RT was having up to five seizures a week.

Lamotrigine was started at 25 mg daily and increased to 50 mg after two weeks and then 100 mg two weeks later. RT's seizures improved, his psychosis resolved and he was discharged. Two weeks later the patient presented to the clinic with a maculopapular rash.

Questions

1. What factors contribute to psychosis in people with epilepsy?
2. Which drug is likely to have caused the rash?
3. What important factors need to be considered in the treatment of psychosis in people with epilepsy?
4. How could this patient's antiepileptic drug therapy be simplified?

Answers

1. What factors contribute to psychosis in people with epilepsy?

Factors that have been shown to contribute to psychosis, include:

- Polypharmacy.
- Complex-partial seizure type.
- Male sex.
- A long history of seizures (14 years in this patient). (The average onset of psychosis occurring with epilepsy is 12–15 years after seizure onset.)
- Vigabatrin and possibly other antiepileptic drugs (AEDS) (McConnell and Duncan, 1998a).

2. Which drug is likely to have caused the rash?

The rash is most likely to have been caused by lamotrigine. The temporal association is striking and lamotrigine is well known to cause rash. Rashes associated with lamotrigine are usually described as maculopapular or morbilliform and occur most commonly in the first eight weeks of therapy. Rash has been reported to occur in up to 11.2% of subjects receiving lamotrigine, although the incidence has been reported to be as high as 18.7% in patients who were taking both lamotrigine and valproate (Gilman, 1995). More serious skin reactions such as Stevens-Johnson syndrome and toxic

epidermal necrolysis occur in only approximately one in every 1000 adults and between one in 300 and one in 100 children (data on file, GlaxoSmithKline). Extreme caution should therefore be exercised.

The development of skin reactions is thought to be related to high initial lamotrigine serum levels. High serum levels are most likely to occur in children or when there are high initial doses. Rapid dose titration or concomitant valproate therapy, and possibly a history of drug allergies or an allergy to another AED, also make rash more likely. Valproate, a known enzyme inhibitor, inhibits lamotrigine's metabolism and prolongs its half-life from a mean of 29 hours to 60 hours. Conversely, enzyme inducers (eg phenytoin, carbamazepine, phenobarbitone), when prescribed with lamotrigine, may reduce its half-life to approximately 15 hours. For these reasons there are three different dosing regimes with lamotrigine therapy. These are for monotherapy, prescription with valproate therapy or prescription with enzyme-inducing drugs without valproate. As RT was receiving valproate, his lamotrigine should have been prescribed at a dose of 25 mg every second day for two weeks, then increased to 25 mg every day for two weeks and then increased by 25–50 mg every one to two weeks, with the usual maintenance dose being 100–200 mg daily.

If rapid dosage titration is thought to be responsible for the rash, it is possible to rechallenge the patient successfully if slow dosage titration is subsequently employed.

3. What important factors need to be considered in the treatment of psychosis in people with epilepsy?

Before an antipsychotic is prescribed to someone with epilepsy it must be decided whether or not the psychosis and seizures are related. If there is a temporal relationship between the seizure and psychosis (peri-ictal psychosis, where the psychosis is apparent either during or immediately after the seizure), the patient is best treated by optimizing their AED therapy (McConnell and Duncan, 1998b). Such patients should not generally be given antipsychotics (which could potentially further lower their seizure threshold, causing more seizures and consequently more psychosis), although occasionally in post-ictal psychosis (psychosis occurring immediately after a seizure) short-term use of antipsychotics may be necessary.

If the psychosis occurs independently of seizures (inter-ictal psychosis), long-term antipsychotic treatment will probably be necessary. Obviously, when choosing an antipsychotic in people with epilepsy, it is important to take into account what effects the drug has on seizure threshold and whether it is likely to interact with any drugs the patient is taking. Once the drug is chosen, it is then important to start at a low dose and increase slowly. This is because changes in doses during initiation, titration and withdrawal of medication (as well as total dose) may all effect seizure threshold (Itil and Soldatos, 1980).

It appears that chlorpromazine is the phenothiazine antipsychotic most likely to lower seizure threshold. Logothetis (1967), after following 1528 patients (with no previous history of epilepsy) who were taking phenothiazines for four and half years, found that chlorpromazine had the highest seizure risk, with 9% of those who received >1000 mg of chlorpromazine a day developing seizures. Toone and Fenton (1977) also found that seizures were more likely to occur with chlorpromazine (mean dose 266 mg) than with other antipsychotics.

Of the typical antipsychotics, trifluoperazine, fluphenazine, perphenazine and haloperidol are thought to be relatively less likely to lower the seizure threshold (Trimble, 1985; Markowitz and Brown, 1987) and haloperidol has been suggested to be one of the antipsychotics of choice in epilepsy (Fenwick, 1995).

Of the atypical agents, risperidone and sulpiride may be the drugs of choice, although olanzapine and quetiapine may also be suitable. Risperidone was associated with only a 0.3% seizure incidence in clinical trials, while sulpiride appears to have minimal effects on EEG; there have been only two case reports of seizures to the manufacturer, Lorex (McConnell et al, 1997).

Although the manufacturers of olanzapine and quetiapine state that the risk of seizures occurring with these drugs is <1% (Lilly SPC, Astra-Zeneca SPC), at least one author (Alldredge, 1999) considers olanzapine and quetiapine to be of intermediate risk for seizures.

Sanofi-Synthelabo, in their summary of product characteristics (SPC), state that seizures have been reported occasionally

with amisulpride. However, as they did not know the incidence of seizures occurring in clinical trials with their drug (personal communication, 2001) caution should be exercised with amisulpride until more information is available.

Clozapine is the most epileptogenic antipsychotic and its effect on seizure threshold is related to both dose and titration rate. Doses <300 mg daily are associated with a 1% seizure risk, while doses >600 mg daily have a seizure risk of 4.4% (Toth and Frakenburg, 1994). Similarly, zotepine has also been associated with a seizure rate of >1%. In one retrospective study (Tscuchiya et al, 1986), the incidence of seizures occurring at zotepine doses <300 mg daily was 2.9%, compared with an incidence of 11.3% at doses >300 mg daily. The manufacturer, however, reports that when used up to a maximum of 300 mg daily the incidence is only about 1% (Orion SPC).

Carbamazepine may lower antipsychotic plasma levels and has been associated with an exacerbation of psychotic symptoms when added to haloperidol (Arana et al, 1986). Conversely, the withdrawal of carbamazepine may increase serum levels, causing extrapyramidal side-effects (Fast et al, 1986). Carbamazepine can also lower serum levels of clozapine and olanzapine (Tiihonen et al, 1995; Lilly SPC) and it has been predicted to lower plasma levels of quetiapine (Astra-Zeneca SPC). Phenytoin and other enzyme inducers may have similar effects (Miller, 1991).

In conclusion, it appears that clozapine, chlorpromazine, loxapine and zotepine are more epileptogenic than other antipsychotics and so should be avoided in people with epilepsy. Risperidone, sulpiride and haloperidol appear to be less likely to lower the seizure threshold. Trifluoperazine, fluphenazine and zuclopenthixol are other alternatives. Caution should be exercised with olanzapine, quetiapine and amisulpride. It is important that only one antipsychotic is given at any one time and that treatment should be initiated with a low dose and increased slowly. AED blood levels should be monitored when an antipsychotic is co-prescribed.

4. How could this patient's antiepileptic drug therapy be simplified?

With respect to AED therapy, more drugs rarely equate to better seizure control. As lamotrigine has most prob-

ably caused a rash in RT, it should be discontinued. Vigabatrin should also be slowly withdrawn, because of the risk that it may be contributing to RT's psychosis. Because carbamazepine and valproate are likely to be at subtherapeutic doses, plasma levels should be taken and their doses optimized. If seizures are controlled, consideration should be given to weaning the least effective of these two drugs (ask the patient) over several months. The vast majority of patients are better controlled on mono- or duo-therapy.

Key points

- Factors that contribute to the development of psychosis in people with epilepsy include polypharmacy, having complex-partial seizures, being male, having a long history of seizures and some anticonvulsant drugs such as vigabatrin.
- It is important to determine whether the psychosis is peri-ictal or inter-ictal before embarking on a treatment regimen.
- Peri-ictal psychosis is best treated by optimizing anticonvulsant therapy.
- Inter-ictal psychosis requires treatment with antipsychotics.
- No antipsychotic is proven not to affect seizure threshold.
- The risk of seizures is dose dependent and related to rapid dose titration; therefore, always start with a low dose and increase slowly.
- Haloperidol, sulpiride and risperidone are three of the safest drugs to use in epilepsy.
- Clozapine, chlorpromazine zotepine and loxapine are most likely to reduce the seizure threshold.
- Be aware of drug interactions which may increase the antipsychotic plasma level.

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7

Treatment of psychosis in pregnancy and breastfeeding

Robyn McAskill

AB, a 28-year-old woman, was admitted to hospital because of a deterioration in her mental state. She believed that she was pregnant and was expressing paranoid delusions that her partner was trying to harm her and her baby. On examination, AB had poor eye contact, was extremely suspicious of the ward staff and was later seen talking quietly to herself while alone. AB was unkempt, very thin and showed other signs of self-neglect. She did not express any suicidal ideation, nor were there signs of self-harm. AB did not know when she had her last menstrual period (LMP).

Her partner reported that there had been a gradual decline in AB's self-care, that she had not been sleeping well and was very irritable with him. Over the past two to three weeks, AB had accused him of trying to harm her and had often locked him out of their flat. He also reported that six months ago they had decided to have a baby.

They discussed it with AB's consultant who agreed to prescribe chlorpromazine instead of her usual depot. AB stopped taking her tablets, probably about four months ago, as they were making her tired and because she feared that the medication would harm her baby.

AB had been diagnosed six years ago as having paranoid schizophrenia. She has had two relapses since then, secondary to non-compliance with oral antipsychotic medication (first haloperidol, then trifluoperazine). During her last admission, three years ago, AB was prescribed Depixol (flupenthixol decanoate) 40 mg every four weeks and procyclidine 5 mg twice daily. Since then AB has remained well on medication.

AB was willing to stay in hospital but did not want to take any medication as 'it will deform my baby'.

A provisional diagnosis of a relapse of a schizophrenic illness was made. A pregnancy test was positive. An ultrasound scan confirmed that AB was approximately nine weeks pregnant.

Questions

1. How should psychosis in pregnancy be managed?
2. Should antipsychotics be continued through labour and delivery?
3. Should AB breastfeed her baby while taking an antipsychotic?
4. Can antipsychotics cause long-term effects on the infant?

Answers

1. How should psychosis in pregnancy be managed?

When prescribing psychotropics to women of childbearing age it is important to discuss the potential effects of both medication and untreated illness on the unborn child and the mother. Advice on family planning should be offered.

It is not clear whether psychotic illness is exacerbated or improved during

pregnancy. Also, controversy surrounds the question as to whether babies born to women with psychoses are at increased risk of malformations independent of drug exposure (Miller 1991; Lee and Donaldson, 1995; Altshuler et al, 1996; Pinkofsky, 2000). One study found that adults with schizophrenia were 12 times more likely to have six or more minor physical anomalies than normal comparison subjects (Ismail et al, 1998). Such anomalies are more likely to be due to genetic factors than antipsychotic drug exposure in vitro.

The pattern of illness experienced by AB is common, with relapses related to non-compliance. AB had discussed her wish to become pregnant with her doctor, but then stopped her oral medication partly because it was making her tired. She and her partner also thought it may harm their baby. Partners may influence a decision regarding medication use in pregnancy, and so it is important that they have a full understanding of the risks of illness and treatment as stated above. Understandably, women may feel a strong sense of determination not to harm their unborn child (Altshuler et al, 1996).

On admission, AB was not sure when her LMP had been. Many antipsychotics cause hyperprolactinaemia which may lead to amenorrhoea and galactorrhoea in some patients. Amenorrhoeic women are unlikely to be fertile, although conception is not unknown. It is important to educate women about these adverse effects, as they may lead to unfounded fears of pregnancy. Moreover, without education, some women with major mental illness may be unaware of a pregnancy until it is well advanced. If pregnancy is suspected, it should be confirmed as soon as possible by taking the patient's menstrual history and a urine sample or serum beta-HCG assay for a pregnancy test. Note that some antipsychotics may produce false-positives in some urine pregnancy tests (Miller, 1991). Physical examination and abdominal ultrasound can then be used, if required, to confirm the pregnancy and estimate gestational age.

It was confirmed that AB is pregnant and she has a provisional diagnosis of a relapse of a schizophrenic illness. At this point the clinician and patient are faced with the difficult task of weighing up the risks of medication during pregnancy against the risks of withholding medication. Obviously, psychotropic

medication should only be prescribed where the benefits to the mother and child are considered to outweigh the risks. All the relevant factors in AB's case should be discussed with her and her partner and all decisions documented fully in the clinical notes.

AB shows signs of self-neglect, paranoid ideation and impulsive behaviour. Untreated symptoms of psychoses can pose a risk to the mother and fetus. Risks include the mother being less able to gain access to prenatal care and make realistic plans for her baby; being more vulnerable to the effects of poor judgement; being less likely to be well nourished; and being more likely to carry out impulsive behaviours including suicide and infanticide (Miller, 1991). The possible impact of untreated symptoms on maternal attachment and child development should also be noted. It is important to consider the patient's previous history together with her insight and social supports. Treatment requires close contact between the patient, their family and the multidisciplinary team. Non-pharmacological treatments such as counselling or psychotherapy should be considered. Organic causes should be excluded.

The main aims of treating AB's relapse include symptom reduction and improving her ability to function so that she is best able to care for herself during pregnancy. Antipsychotics may pose risks during pregnancy as they all cross the placenta freely. Risks include teratogenicity (following first-trimester exposure), neonatal toxicity (if administered close to delivery) and, possibly, more subtle long-term neurobehavioural effects on children and even adults (Trixler and Tenyi, 1997). It should be noted that there are few good quality data on antipsychotropic agents in the treatment of psychoses in pregnancy. Published studies are dated, have methodological flaws and give conflicting results. Most larger studies describe outcomes when older antipsychotics in low doses have been used as antiemetics in the first trimester. Although there are a number of case reports of malformation, including multiple anomalies, no clustering has emerged and there may have been confounding factors in these cases (Miller, 1991; Lee and Donaldson, 1995). Most large observational studies have concluded that women who take antipsychotics during pregnancy are at no higher risk of having a deformed child than women who do not.

Of all the antipsychotics, there are most data on the safety of phenothiazines in pregnancy, particularly chlorpromazine and trifluoperazine, and for this reason these antipsychotics are recommended (Lee and Donaldson, 1995). There is relatively little information on the butyrophenones such as haloperidol, despite their widespread use (Lee and Donaldson, 1995; Altshuler et al, 1996). Two small studies of haloperidol used to treat hyperemesis gravidarum found no association with congenital malformations. Although recommended by some as a treatment of choice (Austin and Mitchell, 1998: Worsley, 2000), caution is required as several case reports associate in vitro exposure to haloperidol with limb malformations (Cohen and Rosenbaum, 1998). There are very few data on other antipsychotics, including atypical antipsychotics, although clinical experience with these drugs is growing. Most data exist for clozapine and olanzapine and, although congenital abnormalities have been reported, it is reassuring to note that no clustering has been found. The bulk of these data is held on file by the manufacturers and has not been published in peer reviewed journals. Such data is inherently biased as abnormal outcomes are more likely to be reported than normal ones and no denominator (number of exposed cases) is available. Atypicals are not absolutely contraindicated and exposure to them in early pregnancy does not warrant termination. Depots should also be avoided because of their prolonged action (making it difficult to adjust doses) and relatively high incidence of adverse effects (Miller, 1991; Lee and Donaldson, 1995). Occasionally depots may be required to ensure compliance but other methods should be tried to achieve this (Worsley, 2000).

Some authors advocate the preferential use of high-potency agents because low-potency antipsychotics such as chlorpromazine may cause orthostatic hypotension, sedation, tachycardia, urinary retention and gastrointestinal slowing. These are theoretical considerations only and there is no evidence of improved outcome with high-potency drugs (Lee and Donaldson, 1995; Pinkofsky, 2000). Benzodiazepines are frequently used to control disturbed behaviour in the setting of psychotic illness. These drugs should be avoided in pregnancy, particularly during the first trimester, as they are probably associated with an

increased risk of cleft palate (Cohen and Rosenbaum, 1998).

When evaluating the risks of medication in AB, it can perhaps be concluded that these are smaller than the risks of untreated illness. AB had found chlorpromazine too sedating. She had responded well to trifluoperazine in the past and so trifluoperazine 5 mg bd was prescribed. This was increased to 5 mg tds after a few days and her symptoms began to resolve after two weeks. In general, the minimum effective antipsychotic dose should always be used and the patient's progress monitored with a recognized rating scale such as the Brief Psychiatric Rating Scale (BPRS). Dosage requirements for symptom control may be altered by changes in drug pharmacokinetics such as absorption, metabolism and volume of distribution during pregnancy.

Adverse effects should be regularly assessed. There are few data on the effects of medications used to treat antipsychotic-induced extrapyramidal side-effects (EPSEs) in pregnancy (Altshuler et al, 1996; Briggs et al, 1998; Pinkofsky, 2000). Diphenhydramine (used in the United States) and anticholinergics have been associated with teratogenicity and therefore should be avoided, at least in the first trimester (Altshuler et al, 1996; Briggs et al, 1998; Pinkofsky, 2000). Anticholinergics can also compound the decreased gastrointestinal motility frequently seen in pregnancy. If EPSEs do develop, dosage reduction or switching to a low potency agent should be tried first. If a drug is still required to treat EPSEs, there is no preferred agent (Miller, 1991; Altshuler et al, 1996).

Maintenance treatment should be considered once AB's symptoms have resolved. Again, the risks and benefits of maintenance therapy should be considered. Obviously, drug discontinuation before or during pregnancy may put the patient at risk of relapse. Maintenance antipsychotics before and during pregnancy should be considered in patients with a history of chronic psychoses and in particular those with a history of repeated episodes caused by drug tapering or non-compliance. Maintenance medication may minimize overall fetal exposure by limiting the need for acute treatment with higher doses of medication, should relapse occur.

2. Should antipsychotics be continued through labour and delivery?

The effects of antipsychotic medication on labour and delivery have not been extensively studied. Single doses of antipsychotics have often been given to reduce anxiety during labour (Robinson et al, 1986) but these drugs can cause postural hypotension, cardiac arrhythmias and sedation. Because of the effects of labour on the cardiovascular system, these adverse effects are relatively more important. Lowered uterine blood pressure due to hypotensive effects of medication may increase the risk of uterine insufficiency (Pinkofsky, 2000). Sedative effects of medication may depress neonate APGAR scores (Pinkofsky, 2000). Also, because antipsychotics lower the seizure threshold, there may also be an increased risk of the consequences of eclampsia (Miller, 1991).

The possibility that the mother may have an elective or emergency caesarean section should be considered. In surgery, hypotensive reactions, cardiac arrhythmias and prolonged sedation have been reported when antipsychotics are given before anaesthesia (Stockley, 1999).

Pharmacokinetic interactions between antipsychotics and opiates, muscle relaxants and general anaesthetics, are not well understood. The inhaled general anaesthetics are metabolized in the liver via CYP2E1 (Naguib et al, 1997). Since most of the typical antipsychotics are metabolized via CYP2D6 (Naguib et al, 1997), the risk of significant pharmacokinetic interactions between these drugs is probably small. Reported interactions are most likely to be pharmacodynamic (eg sedative, hypotensive and cardiac effects) (Stockley, 1999; Naguib et al, 1997).

When antipsychotics are continued throughout the third trimester, adverse effects in the newborn have been reported. For example, antipsychotic discontinuation symptoms may occur. These usually present as agitation, tremor, inconsolable crying, feeding and sleeping difficulties, muscle hypertonicity and poor maturity (Robinson et al, 1986; Lee and Donaldson, 1995; Pinkofsky, 2000). Discontinuation symptoms may appear within three days after birth or may take up to four weeks to appear with long-acting depot preparations (Lee and Donaldson, 1995). The majority are transient and resolve within days,

although there are some reports of symptoms persisting for many months (Altshuler et al, 1996; Pinkofsky, 2000). Other adverse effects reported include: neonatal jaundice in premature infants, colon obstruction, respiratory depression, melanin deposition in the eyes (Simpson et al, 1981; Miller, 1991; Stowe and Nemeroff, 1995; Pinkofsky, 2000; Worsley, 2000).

Some authors recommend slowly withdrawing antipsychotic medication two to four weeks before the expected delivery date to prevent the adverse effects mentioned above. However, this may place the mother at unacceptable risk of relapse. There is also the added risk of puerperal psychosis (Lee and Donaldson, 1995). During the month after childbirth there is a 22-fold rise in the relative risk of psychosis and it is estimated that 50% of women with a previous history of psychosis develop puerperal psychosis.

The effect of puerperal psychosis in the mother on the developing infant is a cause for concern. It is worth noting, should relapse occur, that the mother and baby may be exposed to much higher doses of antipsychotic drugs, since higher doses tend to be used in acute illness.

With respect to AB, it would be prudent to continue her trifluoperazine during labour and delivery, in view of her history of relapse after antipsychotic withdrawal. These issues will need to be discussed with AB and her partner, ideally after her mental state has stabilized. The midwife, obstetrician and anaesthetist (if applicable) should be informed that AB is taking trifluoperazine and the reasons for her continuing it throughout pregnancy. After the birth, AB and her partner need to monitor the baby for adverse effects. AB herself will also need monitoring for signs of recurrence of psychosis (even though she is taking antipsychotic medication). If available, involvement by a specialist mother and baby community psychiatric nurse (CPN) would be useful. AB's general practitioner (GP) and health visitor will also need to be informed that AB is taking trifluoperazine and that adverse effects may develop in the baby.

3. Should AB breastfeed her baby while taking an antipsychotic?

It is widely accepted that, during the first six months of life, breast milk, compared with infant formulas, provides better nutritional and immunological support for the

developing baby. For both the mother and baby there are also psychological benefits to be gained from breastfeeding; it has been shown to assist mother–infant bonding (Buist et al, 1990; Briggs et al, 1998). The general public are very much aware of the advantages of breastfeeding; 42% of mothers continue to breastfeed their babies after the first six weeks of life (Mason, 1998).

All antipsychotics diffuse into breast milk (Buist et al, 1990). This is probably because of their high lipid solubility but may also be because of protein binding, although this is less well understood (Briggs et al, 1998). The baby is at risk of experiencing adverse effects from relatively small amounts of antipsychotic taken in during breastfeeding. Antipsychotic drugs bind to albumin and are largely metabolized by the liver. A newborn, full-term baby has an immature liver, reduced blood albumin concentration and an underdeveloped blood-brain barrier (Chisholm and Kuller, 1997). If the baby is premature, adverse effects are thus perhaps even more likely to occur.

Acute and chronic adverse effects in the baby have not been firmly linked to antipsychotic use during breastfeeding. Some information is available as case reports, but this is often conflicting (Maitra and Menkes, 1996). Adverse effects reported in the baby include: drowsiness, lethargy and extrapyramidal effects (Robinson et al 1986; Maitra and Menkes, 1996; Chisholm and Kuller, 1997).

Less is known about the effects of atypical antipsychotics on the breastfed infant and extra care should be taken to monitor the infant's health. Clozapine should be avoided as it may accumulate in breast milk and there are case reports of 'floppy baby' syndrome. There is also a theoretical risk of agranulocytosis developing in the infant (who is not having regular blood tests).

The decision as to whether AB breastfeeds her baby is a difficult one. The benefits of breastfeeding are well established and continuation of antipsychotic medication, in AB's case, is desirable. However, with respect to the baby, the acute and chronic effects of antipsychotic exposure via breast milk are largely unknown. In this situation, ideally, the clinician should discuss all risks (known and unknown) with AB and her partner and agree a

decision before the start of breastfeeding (ideally before delivery). The overall health of the baby also needs to be considered. If the baby is premature, underweight, has any congenital illness (e.g. cardiovascular malformation), or perinatal complication (e.g. neonatal jaundice), advice from a paediatrician should be sought.

If it is decided that AB will continue her antipsychotic medication and breastfeed her baby, her GP, CPN, midwife and health visitor need to be informed. To minimize the amount of antipsychotic to which the baby is exposed, trifluoperazine should be given as tablets (not sustained-release capsules) as a single dose at night after the last feed. Overnight, AB should be counselled to feed her baby with previously expressed milk or infant formula. This ensures that the baby is not breastfed when the amount of antipsychotic drug in the breast milk is highest. AB and her partner also need to be given some guidance on what adverse effects are possible in the baby and how to manage them (the CPN and health visitor could assist them with this). They also need to understand the importance of child health clinic visits to monitor the overall health and development of the child.

4. Can antipsychotics cause long-term effects on the infant?

In animal studies, fetal exposure to antipsychotics can affect vasculogenesis, neurogenesis, central catecholamine levels and dopamine receptor function. There are conflicting reports of persistent abnormalities in learning behaviour (Kerns, 1986). The extent to which these data can be extrapolated to humans is unclear.

Surprisingly, there is little research regarding neurobehavioural effects from fetal exposure to antipsychotics. Without continuous follow-up, it is impossible to estimate emotional, cognitive and behavioural effects in children who were exposed to antipsychotics in the womb.

Following several case reports of persistent neurobehavioural abnormalities in children, a few larger studies have been published. Two studies (cited in Trixler and Tenyi, 1997) followed children up to the age of five and found no difference in behavioural and intellectual functioning in those exposed in utero to low-dose phenothiazines compared with controls.

Prenatal chlorpromazine exposure was not linked with gross developmental abnormalities in children up to nine years of age (cited in Pinkofsky, 2000). In another controlled study, 68 children exposed to antipsychotics in the second half of pregnancy had their behaviour at school examined. No statistical differences from controls were found (cited in Trixler and Tenyi, 1997). A further study of 151 children exposed to phenothiazines during pregnancy found no difference in IQ scores at four years compared with controls (cited in Kerns, 1986).

These studies represent small samples, generally exposed to low doses of phenothiazines at variable times of pregnancy. Better controlled, more rigorous follow-up studies are needed to draw firm conclusions. Caution is advised.

Key points

- The potential effects of both medication and untreated illness on the unborn child and the mother should be considered.
- Risks include teratogenicity (when taken in the first trimester), neonatal toxicity (if taken up to delivery) and possibly long-term neurobehavioural effects.
- Most large observational studies have concluded that women who take antipsychotics during pregnancy are at no higher risk of having a malformed child than women who do not.
- There is more clinical experience with chlorpromazine and trifluoperazine, and these drugs are generally considered to be safe. Some authors advocate the use of haloperidol, although this is controversial.
- There are few data available on the atypical drugs, but they are not absolutely contraindicated.
- Preterm infants (with very immature hepatic metabolizing capacity) should probably not be breastfed while the mother is taking antipsychotic drugs.
- Women taking clozapine should be advised not to breast feed.
- Exposure of the breastfed infant to antipsychotics can be minimized by administering the drug to the mother as a single daily dose at night after the last feed.

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8

Atypicals and hyperglycaemia

Shameem Mir

KB is a 38-year-old male of Afro-Caribbean origin with a body mass index (BMI) of 24.1 kg/m^2. He was first diagnosed with schizophrenia at the age of 24 and has been stable on flupenthixol decanoate 40 mg every two weeks for the past two years. Although this kept him well, he suffered from persistent parkinsonian symptoms. These symptoms were only partially relieved with anticholinergic medication.

About two months ago, after attending a patient medication group, KB learned of atypical antipsychotics and their lower propensity to cause extrapyramidal side-effects (EPSEs). He discussed treatment options with his psychiatrist, who agreed to a trial of olanzapine.

After 12 weeks of taking olanzapine, KB complained of polyuria. He had gained 4 kg in weight in the first eight weeks of treatment, but lost 2 kg in the last four. Three subsequent fasting-

blood-glucose tests confirmed hyperglycaemia and an oral glucose tolerance test was ordered. Baseline values for blood glucose when KB was on depot medication were not available. KB has no family history of diabetes mellitus.

Questions

1. Can antipsychotic drugs cause hyperglycaemia?
2. Have any risk factors been identified?
3. What is the mechanism of antipsychotic-induced hyperglycaemia?
4. What are the treatment options for KB and how should he be monitored?

Answers

1. Can antipsychotic drugs cause hyperglycaemia?

The prevalence of diabetes in patients with schizophrenia is higher than in the population as a whole. This finding holds true irrespective of whether antipsychotic drugs are taken or not (Mukherjee et al, 1996). In addition, diabetes is known to be more common in African-Americans and Asians than in people of Caucasian origin. Schizophrenia is more prevalent in some ethnic groups, particularly second-generation immigrants of Afro-Caribbean descent (Bhugra and Bhui, 2001). The literature on antipsychotic-induced hyperglycaemia should therefore be interpreted with the above caveats in mind.

Antipsychotic-induced hyperglycaemia was reported in association with phenothiazine derivatives as early as 1964 (Arneson, 1964). It has also been reported with antipsychotics from other chemical groups such as loxapine and with the antidepressant amoxapine (Tollefson and Lesar, 1983).

Until recently, however, hyperglycaemia was not a well-recognized side-effect of antipsychotics. This is reflected in the dearth of published data from before 1994. Since then, with the introduction of the atypical antipsychotics, the number of

reports describing this adverse effect has steadily increased, to the extent that hyperglycaemia is a recognized side-effect of some of the atypical drugs, especially olanzapine and clozapine. One could argue that this is perhaps a result of more vigilant monitoring of drug treatment and that typical drugs may be just as likely to induce hyperglycaemia. However, studies investigating the incidence of hyperglycaemia with typicals versus atypicals are rare.

There appear to be more reports of hyperglycaemia with **clozapine** than with any of the other atypicals. In total, there have been 14 spontaneous reports describing either hyperglycaemia or ketoacidosis in a total of 20 people. The earliest report of hyperglycaemia associated with the use of clozapine was a case described by Kamran et al (1994). A second report, a few months later, described a case of ketoacidosis associated with clozapine (Koval et al, 1994). Since then, there have been an additional 12 reports describing 12 cases of hyperglycaemia and six cases of ketoacidosis (Kostakoglu et al, 1996; Peterson and Byrd, 1996; Koren et al, 1997; Popli et al, 1997; Ai and Riley, 1998; Thompson et al, 1998; Wirshing et al, 1998; Colli et al, 1999; Smith et al, 1999; Isakov et al, 2000; Rigalleau et al, 2000; Wu et al, 2000).

One study has investigated the prevalence of impaired glucose tolerance and diabetes in 63 patients taking clozapine, compared with 67 taking a typical depot antipsychotic (Hagg et al, 1998). In the clozapine group 27% had either Type 2 diabetes or impaired glucose tolerance compared with 9.5% in the depot group. Although numerically large, this difference was not statistically significant.

It is difficult to establish the incidence or prevalence of hyperglycaemia with specific drugs as most of the data relate to single case reports. Importantly, one study has specifically investigated the incidence of treatment-emergent diabetes mellitus in patients being treated with clozapine (Henderson et al, 2000). This was a naturalistic study involving 82 patients who were followed-up for five years. Of the 82 patients, 43 (52.4%) had an increased blood glucose reading at least once and 19 (23.2%) had two or more abnormal glucose values over the five-year period. More importantly, 25 (30.5%) patients were diagnosed with

Type 2 diabetes during the study period.

The first published case report to associate hyperglycaemia with **olanzapine** appeared in 1998 (Fertig et al, 1998). Since then, seven publications have reported a further 11 cases of hyperglycaemia and five cases of ketoacidosis seemingly associated with olanzapine therapy (Wirshing et al, 1998; Gatta et al, 1999; Goldstein et al, 1999; Hayek et al, 1999; Lindenmayer and Patel, 1999; Ober et al, 1999; Rigalleau et al, 2000).

Some case reports describe continuation of hyperglycaemia after withdrawal of the antipsychotic drug, some describe improvement and others a return of glucose tolerance to normal. The more convincing reports describe a deterioration in glucose tolerance after rechallenge (Mir and Taylor, 2001).

There are some published data relating to hyperglycaemia or ketoacidosis associated with the other atypicals. Wirshing et al (1998) described a case of olanzapine-induced hyperglycaemia in a patient who had previously developed hyperglycaemia with **sertindole**. There is a single case report of hyperglycaemia with **quetiapine** (Sobel et al, 1999). There appear to be no published reports relating to **risperidone** or **amisulpride**.

2. Have any risk factors been identified?

It is difficult to establish risk factors for atypical-induced hyperglycaemia from the available literature. This is partly because reports tend to be from either the UK or the USA, and apparent risk factors may differ depending on the nature of the population studied. The demographic and clinical characteristics of 'cases' may be well described, but the characteristics of the population exposed to single drugs is likely to be unknown.

In the present author's review (Mir and Taylor, 2001), some striking similarities between many of the cases reviewed were found and some possible risk factors for clozapine-induced hyperglycaemia were proposed:

- Age of around 40 years.
- Male gender.
- Of Afro-Caribbean or Afro-American origin.

Many of the cases in the review originated from the UK and described people of Afro-Caribbean origin,

although it was recognized that the prevalence of diabetes (and schizophrenia) in this population is higher than in the general population.

Interestingly, although many patients were obese to begin with, a correlation between weight gain and the development of hyperglycaemia could not be found. Weight loss is a symptom of diabetes and was reported in some cases. In addition, a personal or family history of impaired glucose tolerance was not found to be a risk factor for antipsychotic-induced hyperglycaemia.

3. What is the mechanism of antipsychotic-induced hyperglycaemia?

The mechanism of antipsychotic-induced impaired glucose tolerance is not clearly understood and most investigations have involved only clozapine.

Yazici et al (1998) postulated that **insulin resistance** and associated **hyperinsulinaemia** may play a role in clozapine-induced hyperglycaemia. In a larger study, Melkerson et al (1999) came to a similar conclusion; the main difference with their proposal was that the **insulin resistance** was dose related, whereas Yazici et al (1998) found this not to be the case.

More recently, Melkerson and Hulting (2001) investigated insulin levels in those taking olanzapine or clozapine and compared them with a group taking conventional antipsychotics. They found higher insulin levels in those taking olanzapine than in those taking typical antipsychotics, despite similar BMI. For clozapine, they found a direct correlation between plasma concentration and insulin levels. Further controlled studies are needed to confirm the degree and mechanism of impaired glucose metabolism caused by the atypical antipsychotics.

The role of weight gain, as a risk factor in impaired glucose tolerance and cardiac mortality, should not be overlooked.

4. What are the treatment options for KB and how should he be monitored?

In KB's case, a change in antipsychotic medication would be prudent. As there have been no reports of hyperglycaemia with risperidone or amisulpride, they may be considered as preferred alternatives. However, KB has shown sensitivity to EPSEs in the past and may be sensitive to these effects with risperidone or amisulpride.

Quetiapine appears to give rise to placebo-level EPSE (Arvantis et al,

1997) and so far there has only been one published report of hyperglycaemia (Wirshing et al, 1998). This may therefore be a good choice for KB.

Continuing the offending drug and treating the hyperglycaemia may be an option when there is no alternative treatment, e.g. in a patient with treatment-resistant illness where clozapine is indicated.

In Henderson et al's (2000) five-year naturalistic study, all 25 patients who developed diabetes mellitus remained on clozapine and were treated with either an oral hypoglycaemic or insulin.

KB's blood glucose should be monitored before starting the new drug and weekly thereafter for 12 weeks. Indeed, all patients starting an atypical antipsychotic should have a baseline blood glucose value recorded and monthly plasma glucose monitoring for six months. Case reports indicate that this is the period of maximum risk (Mir and Taylor, 2001).

Key points

- Diabetes may be more common in schizophrenia and in those treated with antipsychotics.
- Clozapine and olanzapine appear to be most commonly linked to impaired glucose tolerance and its sequelae.
- Little is known about the mechanisms involved but insulin resistance seems likely to be important.
- Risk factors have not been clearly identified and so close monitoring is advised.

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9

Adherence to antipsychotic medication

Jennie Day

BT, a 46-year-old man who has had a diagnosis of schizophrenia for over 20 years, had again stopped taking both his depot and his oral antipsychotics. BT has had eight previous admissions to hospital and on four of these occasions he had stopped his medication within the previous six months. BT believes that in the past evil spirits had come upon him and made him speak in tongues, and that taking medication is irrelevant to these problems. He has been readmitted on previous occasions while taking medication, reinforcing his beliefs that it is irrelevant to his personal circumstances. BT has religious delusions which are only marginally attenuated by antipsychotics and at present he shows no signs of serious relapse.

Questions

1. What proportion of people with a diagnosis of schizophrenia do not adhere to medication regimens and how does this compare with other populations of medical patients?
2. How does non-adherence affect outcome in schizophrenia?
3. What factors may affect BT's decision to adhere to medication?
4. What strategies improve adherence to antipsychotics?

Answers

1. What proportion of people with a diagnosis of schizophrenia do not adhere to medication regimens and how does this compare with other populations of medical patients?

Reported adherence rates to antipsychotic medication vary widely depending on the patient sample and the method of measuring adherence (Cramer and Rosenback, 1998). Quoted values range between 29 and 90%.

It is generally believed that around 50% of people with a diagnosis of schizophrenia do not adhere fully to medication regimens (Kane, 1985; Kampman and Lehtinen, 1999). Although this figure may seem high, in fact it is no higher than for other groups of people with chronic illnesses such as diabetes or hypertension (Ley, 1992). It is important to recognize that choosing not to take medication is a normal behaviour and qualitative research has shown that the range of health beliefs of people with schizophrenia is similar to people with other long-term conditions (Rogers et al, 1998).

2. How does non-adherence affect outcome in schizophrenia?

Non-adherence to antipsychotic medication is clinically significant. Non-adherence has been associated with an increased rate of involuntary detention, longer hospital admissions and slower recovery from psychotic symptoms (McEvoy et al, 1984). It has been described as the single most important cause of relapse and readmission to hospital (Pool and Elder, 1986) and a

major preventable cause of psychiatric morbidity (Kane, 1983). Indeed, relapse rates have been shown to be up to five times higher in people who choose not to take medication compared with people who adhere to neuroleptic regimens (Robinson et al, 1999). This leads to significant costs to individuals, their families and health-service providers.

However, it is important to stress that adherence is only appropriate if the drug is effective, lacking in distressing side-effects and tailored to the needs of the individual. Given the wide range of serious and distressing side-effects of antipsychotics and the relatively high rate of poor response, it is easy to think of scenarios where choosing not to take medication would be a rational choice. BT is probably a 'partial responder', in that he remains deluded when taking antipsychotics, but may cope slightly better with his delusions. This makes it difficult to argue from a therapeutic viewpoint that adherence is essential for continued well-being.

3. What factors may affect BT's decision to adhere to medication?

The reasons for taking or not taking medication are complex and include illness-related factors, treatment-related factors, patient-related factors and social or cultural factors (Fenton et al, 1997). Perhaps unexpectedly, side-effects of medication and psychotic symptoms have only a minor role in affecting the decision to take antipsychotics. Health beliefs, subjective response to antipsychotics (including dysphoria) and personal attitudes to medication and psychiatry have a greater contribution (Kelly et al, 1987; Awad et al, 1996).

A rating scale devised to measure attitudinal factors that influence adherence (Weiden et al, 1994) describes three subclasses related to adherence (influence of others; belief that medication would prevent relapse; feeling better on treatment) and five subscales related to non-adherence (dysphoria; problems obtaining medication; negative family influence; negative therapeutic alliance; rejection of an illness label). Many workers consider this scale cumbersome and the most widely used scale is the shorter Drug Attitude Inventory which can be self-rated and has been found to predict biochemical measures of adherence (Hogan et al, 1983).

Lack of insight has frequently been cited as an important contributor to non-adherence (eg Bartko et al, 1990),

although the relationship between adherence and insight is more complex than it may at first appear. For example, some patients may continue taking medication even though they have little insight and other patients may have full insight but make an informed choice not to take medication. A number of insight scales include a negative attitude to medication as an indicator of lack of insight, but this overlooks the fact that people can make a logical and informed decision to discontinue medication (eg due to ineffectiveness) independently of insight.

Social conditions and the influence of family and significant others are also important factors. In the case of BT it would be important to find out who are the significant people in his life and what they think of his treatment. This may include family, a partner, people he lives with or people he mixes with, perhaps in a religious organization. One of the most consistent complaints from people within mental health services and their families is a lack of involvement in care and a lack of information, particularly about medication. A large survey carried out by the National Schizophrenia Fellowship (2001) found that 46% of respondents had not received any written information about their drug treatment and 27% had received no verbal explanation from the prescribing doctor. This is despite the fact that the attitudes of staff and in particular the prescriber towards the client and medication are known to influence adherence. The therapeutic alliance between patient and prescriber is an important predictor of adherence (Frank and Gunderson, 1990). Poor interpersonal skills of the prescriber, poor rapport and unresponsiveness to patients' complaints about side-effects have all been found to reduce adherence.

4. What strategies improve adherence to antipsychotics?

There are many studies that have investigated interventions designed to improve adherence to antipsychotic treatment. Most of these studies have used an educational approach, assuming that if people have improved information about medication they are more likely to take it as prescribed. However, whilst this approach often leads to an improvement in knowledge about antipsychotics, it mostly does not lead to an improvement in adherence (Macpherson et al, 1996). Likewise, patients can be informed fully of the

potential to develop tardive dyskinesia as a side-effect of antipsychotic drugs without adversely affecting clinical outcome or adherence to treatment (Chaplin and Kent, 1998). Cognitive behavioural approaches, where the medication is tailored to an individual's lifestyle, have been found to be more effective in increasing adherence (Boczkowski et al, 1985). More recently, Kemp et al (1996) used a motivational interviewing-based intervention 'compliance therapy', which improved adherence, attitudes to treatment, insight and global functioning in people with a diagnosis of schizophrenia. Compliance therapy can prolong survival in community care (ie prevent readmission) (Kemp et al, 1998). Thus, in the case of BT, an open and negotiating approach using such an intervention may be successful in improving his adherence. Although it has been suggested that adherence rates may be better with the atypical antipsychotics, evidence suggests that there is no significant relationship between attitudes to treatment and side-effects (Cabeza et al, 2000). This may be because attitudes to treatment and adherence are complex, and are probably more influenced by socio-cultural factors such as health beliefs rather than clinical factors. More research is needed in this area in order to confirm these findings.

Key points

- Approximately 50% of people with a diagnosis of schizophrenia do not adhere to their medication regimen. This proportion is similar to that found in other chronic illnesses such as diabetes or hypertension.
- Non-adherence increases relapse and rehospitalization.
- Health beliefs, subjective response to antipsychotics, therapeutic alliance, influence of others, insight and side-effects of medication may all have an influence on adherence.
- Education leads to improved knowledge, but has little impact on adherence. Cognitive behavioural approaches have been found consistently to be more effective in improving adherence rates.
- The motivational interviewing-based intervention, 'compliance therapy', has been shown to improve adherence, attitudes to treatment, insight, global functioning and survival in the community.

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10

Depression with anxiety symptoms

Celia Feetam

FM, a 46-year-old man, was admitted to the psychiatric unit of his local district general hospital. FM had experienced breathlessness and severe palpitations, he had felt hot and sweaty and had almost fainted. Although these feelings passed quickly, both FM and his wife had been very frightened by the episode and were concerned that he may have had a heart attack.

On admission FM confessed to having felt under considerable pressure for some time. He had not slept properly for weeks, waking early most mornings and he no longer had a good appetite. He admitted to feeling low, lethargic and lacking in energy and, although once a keen cyclist, FM had not been out on his bike for months, preferring instead to spend his spare time just sitting at home. On further questioning FM said he felt unable to carry on, that 'life was not worth living' and that 'his family would be better off without him'.

When FM left school he had joined the armed forces and seen active service. On discharge he had become a policeman but, although he was very successful and gained rapid promotion, he never liked the work and eventually resigned. He was now in a poorly paid, routine job and had severe financial problems. FM's company had recently relocated to the south of England where he now lived in rented accommodation with his wife and two sons. They had all been reluctant to move and were finding it difficult to settle. His previous medical history was unremarkable. He was taking no regular prescribed medication.

There was no family psychiatric history. FM's parents, although elderly, were alive and well, both physically and mentally. On examination FM appeared thin, tired-looking and somewhat agitated. He did not smoke and drank only very occasionally. Despite his fears that he may have had a heart attack, his ECG was entirely normal, as were his biochemical and haematological results.

Questions

1. What treatment options are available for FM?
2. What factors govern the choice of treatment?
3. What considerations should be given to the way treatment is initiated, continued and, when necessary, eventally discontinued?

Answers

1. What treatment options are available for FM?

This patient is clearly depressed but he is also suffering from anxiety, which in his case is characterized by panic attacks. Up to two-thirds of patients suffering from depression may have associated anxiety symptoms (Clayton et al, 1991). Such anxiety can take the form of psychological or somatic anxiety symptoms, phobias or panic attacks. If depression is the primary

condition then its effective treatment should be sufficient in most cases to relieve concomitant anxiety (Coplan and Gorman, 1990).

An antidepressant is clearly indicated for FM. Either a tricyclic (TCA) or a selective serotonin reuptake inhibitor (SSRI) may be an appropriate choice at this stage, since certain members of both of these groups of drugs have significant anxiolytic properties in addition to their antidepressant effect (Tyrer and Hallstrom, 1993).

Central serotonin (5HT) systems have been implicated in the aetiology of anxiety and panic disorder (Yocca, 1990). Many antidepressants with marked anxiolytic properties inhibit the reuptake of serotonin in the synaptic cleft. This occurs early in treatment, but like the antidepressant effect of these drugs, their anxiolytic effects take some weeks to develop. For the full anxiolytic effect to become apparent, it may be necessary for the $5HT1_A$ inhibitory receptors to be desensitized. This occurs only after continued treatment and it is thought to contribute to an overall increase in 5HT neurotransmission (Cowen, 1997).

The SSRI paroxetine has been shown to be significantly more effective than placebo in the treatment of panic disorder (Oehrberg et al, 1995) as have other SSRIs, citalopram (Wade et al, 1997) and fluoxetine (Michelson et al, 1999). Both paroxetine and citalopram are licensed for the treatment of panic disorder as well as depression. Fluoxetine, sertraline and nefazodone are all licensed for the treatment of depression accompanied by anxiety but not for panic disorder.

Of the tricyclics, clomipramine, imipramine or perhaps amitriptyline may be possible options at this stage (Lydiard and Ballenger, 1987). Their anxiolytic effect may be the result of serotonin reuptake inhibition, or adrenergic alpha $(\alpha)_2$-autoreceptor blockade. In addition, sedation as a result of their H_1 and α_1 adrenergic antagonist activity will also contribute to their anxiolytic effect.

Since most antidepressants take between four and six weeks to show their full clinical efficacy as either antidepressants or anxiolytics it may also be necessary, in the interim, to prescribe a short course of an additional, faster acting anxiolytic such as a benzodiazepine. This would immediately address the anxiety

symptoms, which are likely to be the most troublesome and disabling aspect of the illness for the patient at this time (Cowen, 1997).

Patients with depression prescribed a benzodiazepine in addition to an antidepressant are more likely to show early symptomatic improvement and are less likely to drop out of treatment than those prescribed an antidepressant alone (Furakawa et al, 2001).

2. What factors govern the choice of treatment?

One of the tricyclic group of antidepressants may be considered for FM, largely because of low cost and proven efficacy. FM does not have cardiac problems. His concerns on this matter were very probably part of the anxiety syndrome and the characteristic somatic symptoms of a panic attack. The tricyclics would be contraindicated if this were not the case because of their cardiotoxicity (Jefferson, 1975). FM is not obese or elderly and therefore less likely to be intolerant of any of the anticholinergic side-effects of a tricyclic compound. However, he has exhibited some suicidal ideation, in which case an older tricyclic agent may be hazardous in view of their toxicity in overdosage (Beaumont, 1989). The Fatal Toxicity Index (FTI) is a means of comparing the potential toxicity in overdosage of antidepressants. It is a measure of the volume of prescribing of a drug in the community together with an estimate of the number of deaths attributed to overdose involving that drug. It is defined as the number of associated deaths per million prescriptions. Amitriptyline, for example, has an FTI of 38.94 (Henry, 1997). Of the newer generation, tricyclic antidepressants, either lofepramine or trazodone, may be safer, as they have FTIs of 2.42 and 7.83, respectively. Trazodone is more sedating than lofepramine and may therefore be more suitable for FM, who is agitated and complaining of sleep problems.

While the relative toxicity in overdose of antidepressants should always be considered when prescribing for an individual patient, it should be noted that, from an epidemiological perspective, there is no evidence that prescribing only the newer drugs will reduce the suicide rate. Jick et al (1995) followed a cohort of over 170 000 people who had been prescribed antidepressants at least once by their GP over a five-year period. Although some variables, such as male sex and having received a prescription

for an antidepressant in the last 30 days, were found to be associated with completed suicide, the choice of antidepressant was not. Those patients prescribed lofepramine, fluoxetine and trazodone died by violent means or carbon monoxide poisoning rather than overdose.

An SSRI with anxiolytic properties, such as paroxetine, may, however, be the best choice for FM. Paroxetine, with an FTI of 2.6, would be safe in overdosage. In most patients it is not sedative and is at least as effective an antidepressant as imipramine (Dunbar et al, 1991).

If, after an adequate trial, paroxetine failed to achieve the desired response or was poorly tolerated by FM, venlafaxine, a serotonin and noradrenaline reuptake inhibitor with a more significant effect on serotonin at the lower end of its dosage scale, may be an appropriate alternative. The extended release formulation of this antidepressant has been shown, at a dose of 150 mg daily, to be superior to fluoxetine in the treatment of major depression with concomitant anxiety (Silverstone and Ravindran, 1999). As a result of this and similar studies, extended-release venlafaxine has been licensed in the USA for the treatment of major depression with coexisting anxiety. A licence for generalized anxiety disorder has been granted in the UK.

As an interim measure, a long-acting benzodiazepine with active metabolites such as diazepam, could be used on an 'as required' basis for its speed of action and general efficacy in treating the symptoms of panic disorder and anxiety (Nutt, 1996).

If benzodiazepine dependence and withdrawal were a potential cause for concern in FM, a beta (β)-adrenergic blocking agent such as propranolol could be used. These drugs sometimes alleviate the sympathetic symptoms of anxiety such as sweating, tremor, shortness of breath and palpitations, although they are generally considered to be ineffective in reducing most of the psychological manifestations of anxiety (Bailly, 1996). However, in some cases, where somatic as well as psychological symptoms are present and disabling it may be necessary to combine a β-blocker with a benzodiazepine as a short-term measure.

3. What considerations should be given to the way treatment is initiated, continued and, when necessary, eventally discontinued?

In view of the associated anxiety symptoms, treatment with an SSRI should be initiated cautiously with a low dose, such as 10–20 mg daily of paroxetine, for the first week, together with the chosen short-term anxiolytic agent such as diazepam. This is because an exacerbation of anxiety symptoms and panic frequency is commonly seen during the early stages of treatment with an antidepressant such as paroxetine (Nutt, 1996) and, like the tricyclics, onset of both anxiolytic and antidepressant effects may be delayed for several weeks. Gradual dose titration may be needed to avoid this situation, together with careful reassurance to ensure compliance. Care must be taken to always use a therapeutic dose whichever antidepressant is prescribed.

Treatment at the full, optimum, effective dose, which in view of the associated anxiety syndrome is likely to be at the higher end of the scale for the treatment of a major depression, should continue for at least six months from remission of symptoms (Anderson et al, 2000).

When the decision to discontinue treatment is made it should be done cautiously with a gradual reduction of dosage over a period of two to four weeks (or longer if necessary) to avoid discontinuation symptoms such as dizziness, sensory disturbances, sleep disturbances, agitation or anxiety, nausea, sweating and confusion (Coupland et al, 1996). In respect of the SSRIs, such symptoms are thought to arise as a result of the prolonged desensitization of the $5HT_{1A}$ inhibitory receptors. When the antidepressant is discontinued, the concentration of serotonin may be insufficient to produce an adequate stimulus for these subsensitive receptors. Discontinuation symptoms have also been reported to occur when tricyclic antidepressants, or indeed antidepressants from any class, are discontinued abruptly. The symptom profile and receptor mechanism differs between individual drugs. Withdrawal from paroxetine can be particularly troublesome. The dose should be slowly reduced, usually over a month or more.

Key points

- Up to two-thirds of depressed patients have co-morbid anxiety symptoms.
- If depression is the primary diagnosis, antidepressants should treat the associated anxiety symptoms.
- SSRIs and TCAs can be effective treatments, taking four to six weeks to reach their optimal effect.
- Slow dosage titration may be required to prevent a temporary initial increase in anxiety symptoms.
- Immediate relief may be obtained by the short-term use of a long-acting benzodiazepine.
- Treatment should continue for at least six months after recovery, to prevent early relapse.
- Antidepressant doses should be slowly titrated downwards at the end of the treatment period to avoid discontinuation symptoms.

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11

Sub-optimal use of antidepressants

John Donoghue

EB, a 43-year-old Caucasian woman, was admitted to hospital for the treatment of depression following a domiciliary visit by a psychiatrist. On the ward she appeared quiet and extremely withdrawn, avoided eye contact and responded to questions with monosyllables. Nursing staff reported that she had no interest in any of the activities available: left to herself she sat on her bed all day and stared at the ceiling. She had no appetite and had to be persuaded to take fluids. EB took a hypnotic every night but still woke early every morning. Thyroid function and haemoglobin were normal. She had been prescribed sertraline 50 mg each morning by her general practitioner (GP).

EB's husband said that she had suffered from symptoms like this for over two years, though recently she seemed much worse. She was unable to look after herself or the children any more. Symptoms seem to have become apparent shortly

after the birth of their third child, though the GP assured EB that she was only having 'baby blues' and that these would soon pass. Eventually, the GP did prescribe an antidepressant, but EB was reluctant to take it.

A drug history revealed that EB had been prescribed three different antidepressants: amitriptyline 25 mg twice daily, then dothiepin 75 mg at night, before starting sertraline. Amitriptyline had been prescribed on only one occasion (60 tablets prescribed), dothiepin had been prescribed for two consecutive months, and sertraline had been started only two weeks before the current admission. Between these courses there had been long periods without treatment. Before this EB had been prescribed diazepam for several months, though the GP had been reluctant to continue prescribing because of the risk of dependence.

Questions

1. Discuss EB's treatment with antidepressants by her GP.
2. What factors may influence the outcomes of antidepressant treatment in primary care?
3. What factors may have contributed to the development of a chronic depressive illness?
4. What factors may have influenced the GP's prescribing and the patient's acceptance of antidepressant treatment?

Answers

1. Discuss EB's treatment with antidepressants by her GP.

EB finds herself in circumstances similar to the majority of patients with depression in primary care: only a minority of depressed patients are prescribed an antidepressant and these are rarely used effectively. A recent pan-European study found that only 30% of patients presenting in primary care with depression received treatment with an antidepressant; 17%

received treatment with a benzodiazepine alone (Tylee et al, 1999). An earlier study involving over 25,000 consecutive primary-care attenders found that 10.4% were experiencing a depressive episode, but that only one in four of these patients were given a diagnosis of depression, and that only 13% of those with depression were prescribed an antidepressant (Weiller et al, 1996). In the US, findings from the Medical Outcomes Study revealed that only 23% of depressed patients were prescribed an antidepressant; 30% were prescribed a benzodiazepine (Wells et al, 1994).

Among patients prescribed an antidepressant, few receive treatment at an effective dose for long enough for it to change the course of their illness. Studies in the UK have found that the majority of patients treated with a tricyclic antidepressant (TCA) fail to receive an effective dose (Donoghue and Tylee, 1996; Donoghue et al, 1996; MacDonald et al, 1996). Although patients treated with a serotonin reuptake inhibitor (SSRI) almost always receive a known effective dose, only a minority take the antidepressant for long enough for their symptoms to remit fully (Donoghue, 1998). A large study of over 16,000 depressed patients in primary care found that <3% of patients treated with an older TCA (amitriptyline, dothiepin or imipramine) would receive treatment at an effective dose for four consecutive months. In contrast, patients treated with an SSRI were much more likely to receive effective treatment (odds ratio 17, $p < 0.001$) (Dunn et al, 1999).

2. What factors may influence the outcomes of antidepressant treatment in primary care?

When a diagnosis of depression has been established, and the decision that an antidepressant is the most appropriate treatment taken, it is essential to achieve an effective treatment dose as quickly as possible and, when symptoms have responded, to maintain the same dose for at least six months (Anderson et al, 2000).

Although it has been difficult to conduct dose-finding studies of antidepressants in primary care, the consensus is that older TCAs are ineffective below 75 mg daily, and that a dose of at least 125 mg daily is required to ensure efficacy (Anderson et al, 2000).

Consistently good outcomes have been reported in depressed patients who

received effective doses of antidepressant (Goethe et al, 1988; Rutz et al, 1989; Thase, 1990; Schulberg et al, 1996). Conversely, poor outcomes have been reported in patients receiving inadequate doses of antidepressant (Keller et al, 1986; Goethe et al, 1988; Scott, 1988; McCombs et al, 1990; Isacsson et al, 1994; Ali, 1998).

There is compelling evidence that antidepressant treatment should continue for at least six months following the initial response of symptoms. A relapse rate of 20–25% occurs in patients who continue with antidepressant treatment for six months compared with a relapse rate of 50% in patients on placebo, with most relapses occurring within four months (Anderson et al, 2000).

Reports of inadequate length of treatment with antidepressants have been a feature of the medical literature for the past 25 years. In 1973, a study in the UK found that, within four weeks, 68% of patients had stopped taking their antidepressant (Johnson, 1973). In 1996, in a population of approximately 400,000, over a 14-month period, >85,000 prescriptions for antidepressants were issued to over 20,000 patients, the majority receiving a prescription for a TCA. Antidepressants were prescribed for only short periods of time: 38% patients received treatment for 30 days or less, and 68% of patients had discontinued treatment within 90 days (MacDonald et al, 1996). A five-year study investigating the use of SSRIs in primary care evaluated over 93,000 prescriptions in approximately 27,000 treatment episodes. The length of treatment was inadequate in the majority of patients, with only 31% entering a fourth month of continuous therapy (Donoghue, 1998).

3. What factors may have contributed to the development of a chronic depressive illness?

Adequacy and appropriateness of treatment are regarded as key predictive factors in the development of chronic depression. A review by Scott (1988) proposed that inadequate treatment or absence of treatment predicted the development of chronic depression, and that inadequate treatment is a preventable cause of poor outcome. In a long-term follow-up of 101 patients who had recovered from an index episode of depression, two factors predicting significantly

greater risk of developing chronic depression were observed: one was a longer duration of a previous episode of depression, the other was the length of time before effective treatment was implemented (Keller et al, 1986). In a study of a cohort of patients with chronic depression, multiple linear-regression analysis to investigate factors influencing the development of chronic depression found that the most important predictor of the duration of depressive illness was the time between the onset of symptoms and the introduction of effective treatment, with delayed treatment predicting long episodes of depression (Scott and Eccleston, 1991).

4. What factors may have influenced the GP's prescribing and the patient's acceptance of antidepressant treatment?

Surveys of GPs suggest that their training in this area of therapeutics is inadequate. One survey revealed that 26% of respondents were not able to make an informed choice when prescribing an antidepressant, 14% made no attempt to select an antidepressant to meet individual patient needs, and that <25% would increase antidepressant doses to the maximum specified in the British National Formulary (Matthews et al, 1993). In a second survey, 52% of GPs declared they would prescribe lower than the recommended dose of antidepressant, and 40% would discontinue treatment within four months (Kerr, 1994).

Improving practice in this area has proved to be problematic. One randomized controlled trial that measured the impact on diagnosis rates and patient outcome after delivery of a comprehensive training package found no improvement in either (Thompson et al, 2000).

Other factors that may influence the ways in which GPs prescribe antidepressants include perceptions that patients in primary care cannot or will not tolerate treatment doses of TCAs for long enough periods of time (Thompson and Thompson, 1989), or that, despite evidence to the contrary, GPs believe that their use of antidepressants at low doses is actually efficacious (Thompson and Thompson, 1989; Kendrick, 1996; Fish, 1997; Moore, 1997; Tan, 1997). The high placebo response rate seen in antidepressant drug trials, particularly in patients with less severe depression (Anderson et al, 2000), may be interpreted in clinical practice as a true

drug response, thus reinforcing poor prescribing practice.

There is also evidence that the health beliefs or expectations of patients may prevent them from starting or continuing treatment with an antidepressant (Demyttenaere, 1997). In particular, patients may consider that antidepressants are not appropriate treatments for depression and, as a consequence, may be reluctant to accept treatment initially. They may also be apprehensive regarding the possibility of dependence with antidepressants and be unwilling to continue with treatment for long enough. One study found that patient counselling, including information about depression, increased the proportion of patients continuing to take an antidepressant at three months by a factor of three (Peveler et al, 1999).

Key points

- Antidepressants need to be given at effective doses and continued for at least six months following the initial response.
- The majority of depressed patients in primary care do not receive effective antidepressant therapy.
- Educational initiatives that aim to improve the detection rate of depression and its outcome may not be effective.
- Failure to treat an index episode early and effectively may result in the development of a chronic depressive illness.
- Patient counselling has been shown to increase the proportion of patients remaining on antidepressant therapy at three months.

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Antidepressant prophylaxis and discontinuation symptoms

Stephen Bazire

12

MF, a 48-year-old man, was readmitted to a psychiatric ward via casualty, bringing with him a box of venlafaxine 37.5 mg tablets, labelled 'take one twice a day'. He presented with a withdrawn and apathetic mood, appeared angry but there was no evidence of self-harm and neglect. The diagnosis was a relapse of depression. Although he had a number of social problems, his underlying problem was recurrent, poorly responsive depression, which was becoming chronic. He had been admitted to hospital for the treatment of depression five times in the previous eight years and had been prescribed antidepressants almost continuously since his index episode eight years ago. The treatment plan was to stabilize his mood with venlafaxine 150 mg daily and then discuss his long-term treatment.

MF attended one of the pharmacist-led medication education group sessions on the ward and it became evident that non-compliance with

antidepressants was likely to be a significant factor in his case. One of the reasons given by the patient for his poor concordance with drug therapy was his fear of becoming addicted to antidepressants. This was reinforced by his experiences of adverse events when stopping antidepressants in the past, e.g. feeling as if he had 'flu, 'electric shocks in the head'.

Questions

1. How could you explain that antidepressants are not addictive?
2. Is MF likely to experience withdrawal or discontinuation effects when stopping antidepressants?
3. Is MF likely to relapse if he stops taking antidepressants again?

Answers

1. How could you explain that antidepressants are not addictive?

In a MORI poll carried out in 1991, 78% of the people interviewed agreed with the statement that 'antidepressants are addictive'. For a drug to be properly defined as addictive, or to produce dependence, it must have at least three of seven main features:

1. Tolerance to desired effect
2. Withdrawal symptoms
3. Use greater than needed
4. Inability to reduce the dose
5. Excessive time taken procuring the drug
6. Primacy of drug taking over other activities
7. Continued use despite understanding the adverse effects

One way of explaining to MF that an antidepressant is not addictive is to compare a variety of drugs (both prescribed and non-prescribed, e.g. caffeine, nicotine, alcohol, opiates, amphetamines, etc) in terms of the first three mentioned characteristics and also ask if the drug is used for an immediate effect or taken for a longer term effect to help correct a suspected biological imbalance (see Table I).

Table 12.1

Comparison of dependence potential of a range of medicines and drugs.

	Does the drug produce craving or desire?	*Does the drug produce dependence?*	*Does the drug produce tolerance?*	*Does the drug correct a biological imbalance or is it taken for its immediate effect?*
Alcohol	Yes	Yes, e.g. 'DTs'	Yes	Immediate effect
Caffeine	Yes	Yes, e.g. headaches	Yes	Immediate effect
Smoking	Yes	Yes	Yes	Immediate effect
Amphetamines	Yes	Yes	Yes	Immediate effect
Heroin etc	Yes	Yes, e.g. 'cold turkey'	Yes	Immediate effect
Hypnotics	Sometimes	Sometimes, e.g. 'rebound' insomnia	Sometimes	Immediate effect
Lithium	No	No, if done slowly over 4–12 weeks	No	Correct imbalance
Benzodiazepines	Sometimes but usually not with appropriate use	Sometimes	Sometimes	Correct imbalance and immediate effect
Antidepressants	No	No	Rare	Correct imbalance
Neuroleptics	No	No	No	Correct imbalance

MF will be able to see that classic drugs of dependence produce craving, withdrawal symptoms and tolerance to their desired actions, and are taken for their immediate effect. Antidepressants do not cause craving, generally have few significant withdrawal symptoms and little tolerance develops to their therapeutic effects (although the last two have been reported).

Antidepressants also help correct a presumed chemical imbalance in the brain and have little or no immediate effect.

Sometimes little is gained by this approach: patients may rightly see as addictive any drug which causes withdrawal or discontinuation effects. In such cases, the severity and frequency of discontinuation reactions should be outlined with candour and their brevity emphasized. Antidepressants are potent compounds and need to be treated with respect.

2. Is MF likely to experience withdrawal or discontinuation effects when stopping antidepressants?

Withdrawal or discontinuation reactions

have been reported for many antidepressants upon abrupt withdrawal, as indeed they have for some drugs used in general medicine, e.g. calcium-channel blockers, beta-blockers.

Discontinuation effects have a number of characteristics, e.g. they start within one to two days of stopping (longer for drugs with a longer half-life such as fluoxetine), resolve within 24 hours (often less) of restarting the drug and are common with longer courses or higher doses (Lejoyeux et al, 1996). At least eight weeks' treatment seems to be required before discontinuation symptoms occur, perhaps indicating that they are mediated through the longer term receptor changes induced by chronic antidepressant treatment (Lejoyeux et al, 1996). They can even occur with missed doses, if the antidepressant prescribed has a short half-life. The UK Drug and Therapeutics Bulletin (Anon, 1999) recommends that for less than eight weeks treatment, antidepressants should be withdrawn over one to two weeks. For six to eight months treatment, taper antidepressants over a six to eight week period and after long-term maintenance treatment, reduce the dose by 25% every four to six weeks. Note, however, that some patients prefer to go 'cold turkey' rather than endure mild symptoms over several weeks (discontinuation symptoms are rarely abolished by slow withdrawal).

The main discontinuation symptoms with tricyclics include cholinergic rebound [e.g. headache, restlessness, diarrhoea, nausea and vomiting (Lieberman, 1981)], flu-like symptoms, lethargy, abdominal cramps, sleep disturbance and movement disorders. For selective serotonin reuptake inhibitors (SSRIs), the main symptoms are dizziness, vertigo/light-headedness, nausea, fatigue, headache, sensory disturbance, feelings of electric shocks in the head and limbs, insomnia, abdominal cramps, chills, increased dreaming, anxiety/agitation and volatility (Zajecka et al, 1997). Discontinuation symptoms usually persist for 7–14 days, although in some patients the duration may be many months (Gillespie et al, 1996).

Some SSRIs appear to be associated with more discontinuation effects than others, and a number of comparative studies have been carried out. In a randomized controlled study (n = 242) of short-term discontinuation of maintenance therapy, a five to eight day interruption produced few discontinuation symptoms with

fluoxetine, some with sertraline but most with paroxetine (Rosenbaum et al, 1998). In another similar study some symptoms were detectable even after a second missed dose of paroxetine, with impaired functional performance evident at five days. Again, sertraline was associated with less pronounced changes and fluoxetine with no significant symptoms (Michelson et al, 2000). More recently, rapid discontinuation of citalopram (n = 225) appeared only to produce mild and transient effects (Markowitz et al, 2000). The high prevalence of discontinuation symptoms associated with paroxetine may be because it inhibits its own metabolism and, as serum concentrations fall, less inhibition occurs and levels fall more quickly, leading to a relatively rapid drop in plasma concentration and so drug effect. The CSM recommends slow tapering of paroxetine if discontinuation symptoms occur; i.e. stop, and if problems occur then restart and taper the dose downwards over 12 weeks, with either half-tablet doses or alternate day therapy. In some cases, however, even a four-week gradual discontinuation did not prevent significant symptoms of vertigo, light-headedness and gait instability, and so care is needed (Pacheco et al, 1996). In 1999, the UK Summary of Product Characteristics (SPC) for venlafaxine was changed to include withdrawal reactions from abrupt cessation, dose reduction or tapering of this drug. Reactions included fatigue, headache, nausea, vomiting, dizziness, dry mouth, diarrhoea, insomnia, nervousness, confusion, paraesthesia, sweating and vertigo. These symptoms are very similar to those of the SSRIs (Boyd, 1998). A double-blind, placebo-controlled outpatient study showed that seven of the nine patients who discontinued sustained-release venlafaxine reported the emergence of adverse reactions, compared with two of the nine patients who discontinued placebo (Fava et al, 1997). If venlafaxine is used for more than six weeks, withdrawal over at least one week is recommended by the manufacturers, although longer periods are often necessary.

It is thus quite possible that MF has had discontinuation effects, especially if he has stopped taking antidepressants abruptly in the past or has partially complied with short half-life antidepressants such as paroxetine. This will have reinforced his view that antidepressants are addictive. Patients should be reassured that symptoms tend to resolve over one or two weeks.

Treatment of discontinuation symptoms includes reinstatement at low dose and then tapering (perhaps using diluted syrups if necessary), use of an anticholinergic for symptomatic relief with tricyclics or just letting the symptoms resolve with reassurance (Garner et al, 1993).

3. Is MF likely to relapse if he stops taking antidepressants again?

It is known that 50–85% of people who suffer from one episode of major depression will go on to have further episodes, usually within two to three years if untreated, and that there is a high vulnerability in the early months after recovery.

There are a number of first-episode continuation treatment guidelines and recommendations. The American Psychiatric Association recommends at least 16–20 weeks' treatment at full dose after achievement of full remission, the WHO and the British Association for Psychopharmacology Consensus Committee recommend that treatment is continued for six months or more after recovery (Anderson et al, 2000). Subsequent episodes usually require longer treatment. Continuation doses should be the same as or close to the therapeutic dose (Frank et al, 1993).

Risk factors for relapse include recurrent dysthymia, concurrent non-affective psychiatric illness, chronic medical disorder and a history of relapses. Increasing severity of subsequent episodes is predicted by serious suicide attempts, psychotic features or severe functional impairment (Kupfer et al, 1992). MF is thus at high risk of relapse after recovery and is a long-term risk if untreated.

There are many studies showing prevention of relapse by tricyclics (eg Frank et al, 1993), fluoxetine (Montgomery et al, 1988) and sertraline (Doogan and Caillard, 1992). Probably the best study is by Frank et al (1990), a three-year study with a two-year follow-up (Kupfer et al, 1992). One hundred and twenty-eight patients with recurrent depression (third or more episode of depression) who had responded to imipramine plus interpersonal therapy were evaluated. All were symptom free at the start of the trial. After three years, around 75% of those receiving imipramine remained well compared with <15% receiving placebo. The relapsers in the active-treatment group were mainly non-compliers. Those patients remaining well on imipramine at the end of the original three-year study period were

randomized to continue with active treatment or to receive placebo. After a further two years, 82% of those randomized to receive active treatment remained well, compared with 33% of those who received placebo.

The message for MF appears clear. Antidepressants are effective, they are not addictive and will prevent relapse if taken long-term. Nevertheless, lay perceptions of addiction should be borne in mind and alternative, non-drug treatments for depression should also be made available.

Key points

- Antidepressants do not cause craving and have few significant withdrawal symptoms; little tolerance to their therapeutic effect is seen, and they all help to correct a presumed 'chemical imbalance' in the brain.
- Discontinuation symptoms usually occur one to two days after antidepressants are stopped, and last for seven to 14 days if untreated.
- At least eight weeks' treatment with an antidepressant seems to be required before a significant risk of discontinuation symptoms occurs.
- Shorter half-life drugs are associated with a higher incidence of discontinuation symptoms than longer half-life drugs. Paroxetine and venlafaxine are particularly problematic.
- In a cohort of patients who had suffered from at least three episodes of depression, 75% of those randomized to receive imipramine for three years remained well, compared with <15% of those randomized to receive placebo. This benefit continued for at least a further two years.

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13

Refractory depression

John Whitmore

RD, an unemployed 50-year-old male, is admitted to an acute psychiatric ward following referral from his GP who was concerned that RD was placing his physical health in danger through severe self-neglect. RD's mood is objectively and subjectively low and he has several biological symptoms of depressive illness.

Six years ago, his wife had taken out divorce proceedings against him and one year later he lost his job as a warehouseman after a back injury. He first presented to his GP two years ago, complaining of poor sleep (mainly early morning wakening) and loss of appetite. His GP prescribed paroxetine 20 mg daily but RD returned saying that the tablets made him feel sick. It was then decided that he should start taking amitriptyline.

He was admitted to the ward taking 100 mg amitriptyline at night. This dose was increased to 175 mg nocte but no improvement was observed.

Questions

1. Discuss RD's previous and current antidepressant therapy.
2. Why might paroxetine and amitriptyline have 'failed' to treat RD's depression?
3. List factors which may contribute to RD's depression.
4. What further treatment options are available?

Answers

1. Discuss RD's previous and current antidepressant therapy.

Paroxetine, a selective serotonin reuptake inhibitor (SSRI) is a well-established treatment for depression and is also licensed for anxiety occurring in depression. SSRIs are an appropriate first-line treatment in community-based patients because these drugs are easier to use than tricyclic antidepressants (TCAs) (the starting dose is often the treatment dose) and are less toxic in overdose.

RD's inability to tolerate paroxetine in the early stages of treatment and the perceived lack of efficacy caused him to stop treatment. Side-effects such as nausea are often transient but when coincident with the delay in onset of antidepressant effect may result in poor compliance and treatment failure.

RD was then prescribed amitriptyline. When switching patients from one antidepressant to another the prescriber must be aware of potential problems such as discontinuation syndromes associated with the first antidepressant, and pharmacokinetic and pharmacodynamic interactions due to antidepressant polypharmacy during the crossover period. In this case, unless non-compliance had been confirmed, the dose of paroxetine should be decreased slowly and the dose of amitriptyline titrated from a low starting dose. Paroxetine takes approximately four to seven days to clear from the body, is associated with a relatively high incidence of discontinuation symptoms and may increase amitriptyline plasma levels by up to threefold via inhibition of CYP2D6 and CYP3A4 (the hepatic enzymes responsible for the metabolism of amitriptyline). Tables

summarizing strategies when switching antidepressants are available in the Maudsley Prescribing Guidelines (Taylor et al, 2001).

The choice of TCA is often governed by the side-effect profile of the drug, e.g. sedation, antimuscarinic activity, cardiotoxicity, epileptogenicity. In RD's case it was felt that the sedative properties of amitriptyline might help with sleep problems. It should be noted that RD is described as a regular drinker. Alcohol can potentiate the sedative toxicity of TCAs and should ideally be avoided. This issue should be explored with RD.

2. Why might paroxetine and amitriptyline have failed to treat RD's depression?

The effectiveness of an antidepressant can only be assessed after four to six weeks at a therapeutic dose (Quitkin et al, 1996).

Paroxetine is licensed for the treatment of depression up to a dose of 50 mg daily. RD may have responded to a higher dose of paroxetine given for a longer period of time. His unwillingness to tolerate a dose of 20 mg daily would strongly suggest that non-compliance was a problem. Increasing the dose of paroxetine is thus perhaps not an option worth pursuing, although tolerance can often be improved by retitrating the dose more slowly.

Amitriptyline needs to be given in a dose of at least 125 mg daily to treat depression. RD has been treated with a subtherapeutic dose for 2 months before admission. It is unclear for how long he received a therapeutic dose of 175 mg. If this was less than four weeks, a longer duration of treatment may have been helpful. Therapeutic drug monitoring of plasma levels may be helpful to establish whether a sufficient dose is being prescribed, whether toxicity is likely and to confirm that patients are complying with treatment. However, plasma level monitoring is suitable only to assure adherence, since therapeutic levels are not clearly established and toxicity is better assessed by ECG measurement.

Many patients considered to be treatment resistant may have previously received inadequate doses of antidepressants, especially of TCAs (Donoghue, 1998), or have been poorly compliant.

3. List factors which might contribute to RD's depression.

All patients with apparent treatment-refractory depression should have their diagnosis and previous treatment reviewed. Physical causes such as hypothyroidism should be excluded, as should any other causes that may complicate management.

Many factors may cause or exacerbate depression, such as environment, life events, lifestyle, chronic physical illness and prescribed medication. RD was a regular drinker, divorced and unemployed. He was not known to suffer from any physical problems or take any regular medication.

Adverse life events such as divorce, unemployment and bereavement may also contribute to a person becoming clinically depressed, although it has been reported that response to antidepressants is unaffected by preceding life events in major depression (Tomaszewska et al, 1996). Untreated depression may become chronic (Smith, 1995).

RD's drug treatment to date has been inadequate. It is also possible that RD might have benefited from psychological approaches to managing his symptoms and adverse life events over the previous six years.

4. What further treatment options are available?

If RD fails to respond to, or is unable to tolerate, an adequate dose of a TCA and/or an SSRI for at least four weeks each, antidepressants from another class may be worth trying before considering augmentation agents or electroconvulsive therapy (ECT). However, if two types of antidepressant have been prescribed and taken at full treatment doses for four to six weeks without effect, then augmentation strategies or third-line therapies should immediately be implemented (Anderson et al, 2000).

Perhaps most commonly used is venlafaxine, a serotonin, noradrenaline reuptake inhibitor (SNRI). Venlafaxine is well tolerated, although nausea may occur in the early stages of treatment. This effect may, in some people, be reduced by using the sustained release preparation (XL). At low doses, venlafaxine inhibits serotonin reuptake only but at high doses it also inhibits noradrenaline reuptake. It has been shown to treat depression at doses of between 75 and 150 mg daily. At higher doses

(200–300 mg daily) it has been useful in the treatment of resistant depression and has been shown to be slightly more effective than paroxetine 30–40 mg daily (Poirer and Boyer, 1999). Other studies have also suggested that venlafaxine has useful efficacy in refractory depression.

ECT for treatment-resistant depression is well documented and shown to be effective, but its use requires general anaesthesia. Poor public perception has led to many patients not giving the required consent. Around half the treatment-resistant patients given ECT respond in the short term, but half this group relapse after six to 12 months (Potter and Rindorfer, 1993).

Lithium, liothyronine and tryptophan are used as augmentation agents and their use is supported in both the literature and clinical practice. If monotherapy with two or more antidepressants has been tried, augmentation with one of these drugs may be considered.

Lithium has been found to be effective at plasma levels of 0.4–0.6 mmol/l. Augmentation of a variety of TCAs and SSRIs has been reported (Bauer and Döpfmer, 1999). However, therapeutic drug monitoring is essential to ensure therapeutic levels and avoid toxicity. Renal and thyroid function must also be monitored initially and at regular intervals if lithium is to be used long term.

Liothyronine (T_3) augmentation, at doses of 25–50 μg daily for a minimum of four weeks has been shown to improve the response to antidepressants in refractory depression. Thyroid function monitoring is essential and it has been shown that patients with subclinical hypothyroidism responded to augmentation with thyroxine (T_4) (Targum et al, 1984); euthyroid patients showed a higher response rate with liothyronine (Joffe and Singer, 1991). However, prolonged treatment with liothyronine may lead to hypothyroidism when discontinued.

Tryptophan, an amino acid precursor to serotonin, is more widely used as an augmentation agent than as monotherapy. It is well tolerated and its use documented widely (Smith, 1998), especially in conjunction with TCAs and monoamine oxidase inhibitors (MAOIs). Associations with eosinophilia–myalgia syndrome mean that patients must be registered with

the manufacturers and regularly monitored. Combinations with SSRIs could potentially lead to 'serotonin syndrome'.

Combinations of different classes of antidepressants have been tried (Amsterdam and Hornig-Rohan, 1996) but there is potential for problematic interactions. They should only be initiated, with caution, by experienced psychiatrists with close monitoring for adverse events.

TCAs and MAOIs have been found, for many years, to be effective for some treatment resistant depressives (Marley and Wozniak, 1983). This strategy has waned in popularity since the introduction of the newer antidepressants. Fatalities have been reported following the combination of tranylcypromine and clomipramine. Other combinations may lead to adverse effects.

TCAs and SSRIs have been tried together but there is a high risk of adverse interactions. Some SSRIs may increase plasma levels of certain TCAs significantly, by inhibiting the metabolism of the latter. It is possible that some of the reports of increased efficacy may be due partially to therapeutic TCA levels being reached. If these two classes of antidepressants are to be coprescribed, the safest choice of SSRI would appear to be citalopram, or low-dose sertraline, which have little or no effect on the metabolism of TCAs (Taylor, 1995).

'Triple therapy' has also been tried, one example being clomipramine, tryptophan and lithium.

Combinations of drugs acting separately on noradrenaline and serotonin may be worthy of consideration but the safety of combinations of reboxetine and SSRIs is not well documented.

The use of the following drugs to augment antidepressants has been reported, although the evidence is variable, some being limited to case reports. **Pindolol** (5 mg tds) is well tolerated. Research shows some possible clinical use. Studies in the UK have shown an improved response rate compared to antidepressants alone, with a more rapid onset of action (Perez et al, 1997). However, American trials have not repeated this (Berman et al, 1997). It is thought that this may be due to the availability of single isomer preparations in the UK as opposed to

a mixture of isomers in the USA. **Dexamethasone**, given either as a 'stat' dose or short course, has shown improvements in antidepressant response in some cases. One report showed that six out of 10 fluoxetine-resistant patients improved with dexamethasone augmentation (Dinan et al, 1997). **Buspirone** has been used to augment fluoxetine but results in treatment-resistant depression appeared unpromising (Fischer et al, 1998). However, the anxiolytic activity of buspirone may well have helped counter any anxiety exacerbated by fluoxetine. Similarly, **clonazepam** has been reported to improve outcomes when used to augment fluoxetine alone. The authors suggested that the anxiolytic effects may reduce the severity of depressive symptoms and partially suppress SSRI side-effects (Smith et al, 1998).

Antiepileptic drugs have also been tried. **Lamotrigine** may possibly have an antidepressant effect, as monotherapy in bipolar disorder and as an adjunct in major depression (Maltese et al, 1999). **Sodium valproate** has been used to augment TCAs, but the evidence for carbamazapine in treatment-resistant depression is poor. Antiepileptic drugs are more often used in bipolar depression.

Low folate levels have been associated with depression and non-response to antidepressants. It may be useful to monitor folate levels when assessing for treatment-resistant depression.

Other drugs which may be useful for treatment-resistant depression include: atypical antipsychotics, amphetamines, bromocriptine, captopril, cyproheptadine, inositol, ketoconazole, levodopa, pergolide, thyrotrophin-releasing hormone, selegiline and verapamil; but evidence is often anecdotal with low numbers of patients being exposed. Interactions between these drugs and some antidepressants must also be considered, e.g. MAOIs with amphetamines and levodopa, and moclobemide plus selegiline with high tyramine content foodstuffs.

Non-drug strategies, e.g. sleep deprivation, bright light therapy, psychosurgery, have been discussed by Singh (1995).

Key points

- Antidepressants need to be prescribed at a therapeutic dose and patients assessed after four, preferably six, weeks.
- Caution must be exercised when switching antidepressants to avoid discontinuation effects and drug interactions.
- Before diagnosing treatment resistance, patients should have been tried on at least two classes of antidepressant.
- Non-drug measures may also be useful in treating treatment-refractory depression.

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Treatment of depression in people with epilepsy

Denise McConnell

14

SC, a 25-year-old Caucasian woman who has a 10-year history of complex partial seizures with a temporal lobe focus and secondary generalized seizures, was seen in casualty 12 hours after a flurry of secondary generalized tonic clonic seizures. She presented with acute suicidal thoughts and severe depression. Symptoms included anhedonia, loss of appetite, sleep disturbance, loss of sexual desire and suicidal ideation. Her GP had diagnosed depression one month previously and had prescribed dothiepin. SC was unemployed, precluded from driving because of her epilepsy and had recently broken up with her long-term boyfriend. Her medication at presentation was:

Dothiepin	*225 mg nocte*
Carbamazepine	*200 mg nocte (plasma level = 4 mg; range: 4–12)*
Primidone	*250 mg nocte*

Questions

1. What are the contributing factors for depression seen in SC and what other contributing factors are there in people with epilepsy?
2. What factors may have contributed to her recent flurry of seizures?
3. What are the important factors to consider in the treatment of depression in people with epilepsy?

Answers

1. What are the contributing factors for depression seen in SC and what other contributing factors are there in people with epilepsy?

The causes of depression in epilepsy are complex and may be related to the treatment of SC's epilepsy, to psychosocial factors, to an underlying pathology causing both the seizures and the depression or may be unrelated to epilepsy. Some of the drugs used in the treatment of epilepsy can cause depression, either directly or indirectly. For example, phenobarbitone and primidone (which is metabolized to phenobarbitone) directly cause depression. Depression resulting from antiepileptic drug (AED)-induced folate deficiency or from stigma resulting from the appearance and social embarrassment of gingival hyperplasia caused by phenytoin are examples of indirect effects.

Psychosocial factors include stigma and public perceptions, restrictions on driving, difficulties in gaining employment and self-esteem issues. Structural, developmental or genetic abnormalities may be responsible for both seizures and depression but, of course, SC may have simply developed a primary depressive illness (McConnell and Duncan, 1998).

Factors which may have been responsible for SC's depressive illness include stigma, unemployment, being prevented from driving, her recent relationship break-up, primidone therapy, epilepsy with a temporal lobe focus and loss of seizure control.

2. What factors may have contributed to her recent flurry of seizures?

Factors which could have contributed include:

- A subtherapeutic carbamazepine level. Even though her plasma level of 4 mg/l is within the reference range for carbamazepine, this is not controlling her seizures. The dose should be titrated upwards to maximize control. Note also that once-daily administration of carbamazepine, particularly in a patient receiving an enzyme-inducing drug such as primidone, is highly unlikely to lead to therapeutic blood levels over a 24-hour period.
- SC's recently prescribed dothiepin. Tricyclic antidepressants (TCAs) can lower the seizure threshold, especially if they are started at too high a dose and increased too quickly. SC's dothiepin plasma level should be measured.
- Stress, such as the recent break-up of her relationship.
- Primidone inducing carbamazepine's metabolism and thus lowering its plasma level (if primidone had recently been added to SC's carbamazepine therapy).
- Depression, possibly increasing seizure frequency. A causal relationship is not certain.
- Lack of adherence to her prescribed anticonvulsants. Although there is no direct evidence in this case, missed medication is one of the common causes of seizure exacerbation and should always be considered.

3. What are the important factors to consider in the treatment of depression in people with epilepsy?

Before an antidepressant is prescribed to someone with epilepsy it is essential to determine whether the depression has a temporal relationship with the seizures (peri-ictal) or whether it has occurred independently of the seizures (inter-ictal). In peri-ictal depression it is important to optimize AED therapy and not to give an antidepressant that could further lower the seizure threshold and thus contribute towards further depressive episodes. In inter-ictal depression an antidepressant should be chosen that is less likely to lower the seizure threshold, or to interact with any prescribed medication, or cause unacceptable adverse effects.

Seizures are an infrequent but important adverse effect of most, if not

all, available antidepressants. Risk factors for antidepressants causing seizures include epilepsy or a previous history of seizures, head injury or loss of consciousness; known EEG abnormalities; a history of substance abuse or withdrawal from alcohol or anxiolytics; dementia; a recent or rapid dose escalation of the antidepressant; and high plasma levels of the drug or its metabolites. [For a full review see McConnell and Duncan (1998).] Some antidepressants may also be more likely to induce seizures in a given individual. As there are no comparative studies examining antidepressants in epilepsy with respect to seizures, it is necessary to use animal, clinical trial, EEG and overdose data, case reports, prescription event monitoring and reports from the Committee on Safety of Medicines (CSM) to evaluate the seizure potential of a given antidepressant.

If all of the above are considered, it appears that the selective serotonin reuptake inhibitors (SSRIs) and moclobemide are less likely to lower the seizure threshold than TCAs (McConnell and Duncan, 1998). Of the TCAs, it appears that dothiepin may be one of the more epileptogenic. In one overdose study, dothiepin was much more likely to cause seizures than were other TCAs (Buckley et al, 1994), although this was probably at least partly because those patients who had taken dothiepin had consumed much larger doses than those patients who had taken other TCAs. Figures from the United States indicate that dothiepin has a higher incidence of seizures (0.89%) than other TCAs (0.5%) (de Jonghe and Swinkles, 1992). Clomipramine also appears to be one of the more epileptogenic antidepressants. In one study a seizure incidence of 1.04% was found (Waalinder and Feighner, 1992), although seizure rates have been quoted as being 0.48–2.1%, with the highest risk occurring on doses >300 mg daily (Stimmel and Dopheide, 1996). Dothiepin and clomipramine should be avoided in people with epilepsy. If a TCA is to be given, doxepin may be the drug of choice. In a study in which doxepin was given to people with epilepsy, seizure frequency increased in only two of 19 patients, whereas 15 patients had a decrease in seizure frequency and in two it was unchanged (Ojemann et al, 1983).

If an SSRI is to be chosen, there is some evidence that fluoxetine, sertraline and citalopram are less epileptogenic and

fluvoxamine (and possibly paroxetine) more epileptogenic (McConnell and Duncan, 1998; Hovorka et al, 2000). Of these agents, only citalopram has been looked at in prospective studies and none have been subject to randomised controlled studies in people with epilepsy. In the first of these studies, citalopram was given to 43 patients in doses of 10–40 mg and at the end of 8 weeks, seizure frequency did not worsen when compared to the frequency during the two months prior to citalopram treatment (Hovorka et al, 2000). A second open trial of 16 patients receiving 20 mg/day over 4 months also found no deterioration in seizure status (Specchio et al, 1997). Both these studies were underpowered and of too short duration to draw firm conclusions.

Of the newer antidepressants, mirtazapine appears promising, with only one case of seizures being reported in clinical trials out of a population of 1378; giving an incidence of <1 in 1000 (personal communication, Organon, 1999). Overdose data also looks favourable, again with only one case of seizures reported (on accidental overdose in a four-year-old girl) out of 63 spontaneous reports to the manufacturer (personal communication, Organon, 2001).

Bristol-Myers Squibb do not have a stated seizure incidence for nefazodone (SPC, 2001), although in pre-marketing trials only one patient had a recurrence of petit mal seizures and there is one report of seizures occurring in overdose (a multidrug overdose; Alldredge, 1999). This led the author to classify nefazodone as having a low relative risk for seizures.

Overdose data for trazodone suggest that it may also be a drug that is less likely to lower the seizure threshold (Wedin et al, 1986) and could be a useful antidepressant if sedation is required.

In pre-marketing trials 3 confirmed seizures and one unconfirmed seizure occurred in 2258 patients on venlafaxine (personal communication, Wyeth, 2001). In these trials venlafaxine demonstrated a risk of 0.5 seizures per 100 patient-years of drug exposure compared with a rate of 1.5 amongst the active comparator drugs (imipramine, trazodone, amineptine, clomipramine, maprotiline and dothiepin; 2 of 591 patients). There have also been 125 reports of seizures

to the CSM (1995 to May 2001) (personal communication, Wyeth, 2001). Even though the quality of the data for venlafaxine are much better than for other antidepressents the risk of epileptogenesis is still uncertain at this time although it is considered to have an intermediate relative risk (Alldrege, 1999).

In trials involving 1500 patients on reboxetine there were two reports of seizures (0.13%; personal communication, Pharmacia & Upjohn, 2001) and these represent too few data for any conclusions to be made about epileptogenicity.

Once it has been decided which antidepressants are safest with respect to seizure threshold, potential drug interactions need to be considered. As carbamazepine is metabolized by cytochrome p4503A4 (CYP3A4), any drug that is metabolized by, or is an inhibitor or inducer of, CYP3A4 could potentially interact with carbamazepine. For instance, norfluoxetine (the principal metabolite of fluoxetine) is a moderate inhibitor and nefazodone a potent inhibitor of CYP3A4. Fluoxetine and nefazodone would therefore be expected to increase carbamazepine plasma levels. Indeed, fluoxetine has been shown to increase carbamazepine plasma levels by up to 60%, resulting in carbamazepine toxicity (Pearson, 1990). These drugs should therefore generally be avoided in patients taking carbamazepine.

Sertraline is thought to be less likely to raise carbamazepine plasma levels. Nevertheless, there has been one report in which carbamazepine plasma levels were increased by 80% within four weeks of sertraline 100 mg being started (Joblin and Ghose, 1994). Fluvoxamine has also been reported to increase carbamazepine plasma levels (Fritze et al, 1991).

Another AED with a narrow therapeutic index is phenytoin. Phenytoin is metabolized by CYP2C9 and CYP2C19 and thus fluoxetine, a known inhibitor of CYP2C19, could increase phenytoin plasma levels. This has been borne out in practice (Jalil, 1992; Woods et al, 1994). Serum levels need to be monitored closely. Sertraline (Ciraulo et al, 1995) has also been reported to raise plasma levels, although not to a clinically significant degree, and there is an unpublished study of paroxetine increasing phenytoin levels [cited by McConnell and Duncan (1998)]. Although fluoxetine is the drug most

likely to interact with both carbamazepine and phenytoin (and nefazodone with carbamazepine), plasma levels of these two AEDs should be monitored closely after the addition of any new antidepressant, since pharmacokinetic interactions can rarely be discounted.

Conversely, it is possible that the AED enzyme inducers (carbamazepine, phenytoin, phenobarbitone and primidone) could lower antidepressant plasma levels, and sodium valproate, an enzyme inhibitor, could increase antidepressant plasma levels. Certainly, carbamazepine may reduce plasma levels of nefazodone and hydroxynefazodone by 95%, making nefazodone ineffective.

Both valproate and, to a lesser extent carbamazepine, can cause weight gain and many of the AEDs can cause drowsiness. It may be preferable to choose an antidepressant that is less likely to cause these adverse effects, namely an SSRI.

If we consider all of the above, the antidepressants of choice in people with epilepsy are fluoxetine (if there are no interacting drugs, or if careful monitoring is available), sertraline, citalopram and moclobemide. Monoamine oxidase inhibitors (MAOIs) may also be suitable but should, in theory, not be given with carbamazepine. Trazodone is an option if sedation is required. If a TCA is required, doxepin is probably the drug of choice.

Key points

- Underlying physical pathology, psychosocial factors and anticonvulsant drugs may all contribute to the development of depression in people with epilepsy.
- It is important to determine whether the depression is peri-ictal or inter-ictal before embarking on a treatment regimen.
- Peri-ictal depression should be dealt with by optimizing anticonvulsant cover.
- Inter-ictal depression necessitates the use of antidepressants.
- SSRIs, MAOIs and moclobemide are less epileptogenic than tricyclics.
- Potential drug interactions between anticonvulsants and SSRIs should be considered.

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15

Treatment of depression in cardiovascular disease

Eromona Whiskey

BL is a 67-year-old Caucasian man with a long history of hypertension. Two months ago he suffered a myocardial infarction (MI). He was treated and subsequently discharged from hospital. BL had in the past 15 years been treated twice for depression, each time with amitriptyline 100 mg daily. His wife reported that, this time, he had not bounced back the way she thought he would. He had trouble sleeping, lacked motivation and had no energy. BL's GP decided to refer him to the psychiatric team because of severe depressive symptoms. His current medication was:

Aspirin 75 mg od
Atenolol 50 mg od
Simvastatin 10 mg od
Enalapril 10 mg od

The psychiatric team decided to prescribe fluoxetine 20 mg for BL.

Questions

1. What is the relationship between depression and cardiac disease?
2. What are the aims of antidepressant treatment for BL?
3. What are the primary considerations in selecting an antidepressant for BL?
4. Which alternative antidepressant would be suitable for BL?
5. How should BL's antidepressant treatment be monitored?

Answers

1. What is the relationship between depression and cardiac disease?

Following a MI, up to 20% of patients meet criteria for major depression (Anon, 1996) compared with a prevalence of about 5% in the general population. The risk of dying within six months of a MI is significantly greater (four times) in depressed patients than patients who are not depressed (Frasure-Smith et al, 1993). The risk of ischaemic heart disease (IHD) is also greater in patients with depression. In addition, several studies document increased cardiovascular morbidity and mortality in patients with depression (Glassman, 1998; Nemeroff et al, 1998).

The complex relationship between depression and cardiac disease is only partially understood, although several mechanisms have been proposed. One of the most widely cited is that depression alters cardiac autonomic tone which, in turn, predisposes to ventricular arrhythmias and sudden cardiac death (Carney et al, 1999). Another proposed mechanism is increased platelet reactivity. There is evidence that there is enhanced platelet activation and responsiveness in depressed patients compared with non-depressed patients, which may increase the risk of MI (Musselman et al, 1998).

An association between fatal MI and antidepressant use has also been reported by various authors (Penttinen and Valonen, 1996; Ottervanger et al, 1997; Cohen et al, 2000). Penttinen and Valonen (1996) noted a fivefold increased risk of MI among users of antidepressants in a cohort of 3172

male Finnish farmers. In a later study, Cohen et al (2000) found the increased risk was only associated with tricyclic antidepressant (TCA) use and not serotonin reuptake inhibitors (SSRIs). Whether this increased risk is due to depression, antidepressant use or the presence of other risk factors remains unknown.

The complexities of this area are increased by the observation that certain drugs used in the treatment of cardiovascular diseases, especially lipophillic β-blockers such as propranolol, have been linked with depression, although the link appears to be tenuous (Thiessen et al, 1990; Gerstman et al, 1996).

2. What are the aims of antidepressant treatment for BL?

Since depression may be a negative prognostic risk factor in patients recovering from MI, it may be argued that treatment with an antidepressant will prevent mortality and improve survival in post-MI patients. However, there is no evidence to date that treatment with an antidepressant improves survival (Carney et al, 1999). Indeed, there is a possibility that antidepressant use might increase mortality.

Although research is still limited, there is some evidence that depressed patients are less likely to adhere to treatment. Thus, for example, depressed post-MI patients are more likely to drop out of exercise programmes (Blumenthal et al, 1982). Therefore, the aim of treatment is to reduce suffering, improve quality of life and enhance adherence to medical treatment and rehabilitation.

3. What are the primary considerations in selecting an antidepressant for BL?

The primary considerations in selecting an antidepressant are:

- Cardiac safety
- Tolerability
- Potential drug interactions

Cardiac safety

Antidepressants have a variety of cardiovascular effects, including effects on heart rate, blood pressure, cardiac rhythm, contractility and conductivity. Therefore, in patients with pre-existing cardiac disease, safety considerations are the overriding consideration in the choice of antidepressant.

TCAs are contraindicated because of their adverse cardiovascular profile.

They cause orthostatic hypotension, affect cardiac conduction, prolong QTc interval, have proarrhythmic activity, increase heart rate and are lethal in overdose. In the Cardiac Arrhythmia Suppression Trial (CAST, 1989) in 1987, it was found that antiarrhythmic drugs like flecainide caused a three-fold increase in mortality following an MI. Because TCAs have a similar antiarrhythmic activity, it is possible that they carry a similar risk (Roose and Glassman, 1994)

The SSRIs appear to have a benign cardiovascular profile and are considered the drugs of choice in patients with cardiac disease (Fisch, 1985; Roose et al, 1998; Cleophas, 1997; Rasmussen, 1999). There are only isolated reports of fluoxetine causing adverse cardiac side-effects (Ellison et al, 1990; Buff et al, 1991).

Information regarding the use of the new generation antidepressants is still very limited, although some agents such as mirtazapine and nefazodone appear promising alternatives (Montgomery, 1995; Robinson et al, 1996). Venlafaxine and reboxetine may affect heart rate and blood pressure, and can very rarely cause cardiac rhythm abnormalities.

Tolerability

The elderly patient in particular has an increased sensitivity to side-effects, such as orthostatic hypotension, anticholinergic effects and sedation, which may compromise treatment. Results from clinical trials and experience from clinical practice comparing TCAs with SSRIs show that SSRIs have a better tolerability profile. Treatment discontinuation is frequently higher among patients treated using TCAs. In practice, many clinicians are therefore hesitant to prescribe sufficiently high doses of TCAs in elderly patients because of poor tolerability, which can result in the use of subtherapeutic doses and untreated depression.

Drug interactions

Many drugs are used following MI. These include aspirin, β-blockers, calcium-channel blockers, lipid-lowering drugs, digoxin, angiotensin-converting-enzyme (ACE) inhibitors, nitrates and warfarin. The choice of antidepressant will therefore depend on any potential drug–drug interactions. Fluoxetine, paroxetine and fluvoxamine are potent inhibitors of the cytochrome P450 system, whereas citalopram and

sertraline have weak inhibitory effects (Greenblatt et al, 1998). For example, there are reports of chest pain, bradycardia and possible heart block with SSRI-β-blocker combinations. Warfarin interacts with various antidepressants, leading to unpredictable changes in the International Normalised Ratio (INR) (Duncan et al, 1998). Furthermore, aside from pharmacokinetic interactions, care must be taken to consider any pharmacodynamic interactions, e.g. enhanced hypotensive and sedative effects.

Two weeks into treatment, BL developed a rash possibly caused by fluoxetine. The antidepressant was therefore withdrawn.

4. Which alternative antidepressant would be suitable for BL?

Sertraline would be a suitable alternative. This is the only antidepressant which has so far been studied in the treatment of depression in post-MI patients. In a small study, Shapiro et al (1999) demonstrated the efficacy of sertraline in 24 patients meeting criteria for depression after an MI. After 16 weeks of treatment, the mean sertraline dose 79.8 mg, 15 of 24 patients (62.5%) were considered responders.

In the event that BL does not respond to, or poorly tolerates, sertraline, what are the options? This question can only be addressed after a careful risk-benefit assessment. In the first instance, data on the efficacy of SSRIs in depressed elderly patients with cardiac disease is limited, although the studies that do exist are generally favourable (Evans et al, 1997; Strik et al, 1998). Secondly, there are some data to suggest that the TCAs are more effective than SSRIs in more severely depressed patients (Andersson, 2000). For BL, therefore, the options would include antidepressants such as trazodone, nefazodone or mirtazapine. Alternatively, a TCA such as nortriptyline, which is considered to have the least cardiovascular effect of the TCAs (Warrington et al, 1989), may be considered.

The decision must, however, be based upon a careful assessment of the severity of depression against the cardiac risks associated with antidepressant treatment.

5. How should BL's antidepressant treatment be monitored?

BL should be monitored for response to treatment, tolerability and side-effects. In particular, blood pressure and heart rate should be regularly assessed.

Adherence to prescribed medicatison should be encouraged. BL should be observed for bruising, bleeding or disturbances of coagulation, as these have been associated with SSRIs (de Abajo et al, 1999). BL is also receiving aspirin, which may increase this risk.

Key points

- Depression is common post-MI and is a cause of increased morbidity and mortality.
- There is an increased incidence of cardiovascular disease in people with depression.
- Most antidepressant trials exclude patients with cardiac disease.
- SSRIs are the antidepressants of choice in patients with cardiac disease.
- Cardiac safety, tolerability and drug interactions are the main considerations.
- TCAs, venlafaxine and reboxetine should be avoided.

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Panic disorder

Celia Feetam

16

TF, a 30-year-old male architect, was admitted to a psychiatric unit following an outpatient consultation with his psychiatrist.

TF had a long history of generalized anxiety disorder (GAD) with panic attacks, and had been admitted to hospital several times. His last admission was some four years earlier when he responded well to imipramine, group therapy and anxiety management.

On admission, TF was clearly extremely anxious, but there were no psychotic symptoms and his memory was intact. All aspects of a physical examination were entirely normal except for a raised but regular pulse. Biochemistry and haematology tests were also normal. There was no history of any relevant past physical illness. Both his ECG and EEG were normal. He neither smoked nor drank significant amounts of alcohol.

For several months before this admission TF had been reasonably well maintained on:

SR Propranolol	80 mg daily
Sertraline	50 mg daily
Diazepam	10 mg three times daily

This regimen had reduced the frequency of his panic attacks but there had always been a background anxiety which had increased significantly over the past three to four weeks to the extent that he now found it difficult to concentrate or to function normally.

TF complained of always feeling low and agitated. He had frequent attacks of hyperventilation and suffered severe palpitations with the result that he was no longer able to work and rarely left his home. On admission, his speech was rapid and garbled. He was breathless at rest and demonstrated vasomotor lability.

On admission the propranolol and sertraline were stopped but diazepam was continued at the same dosage.

In view of the duration and severity of his symptoms and his previous drug history it was decided to try a monoamine oxidase inhibitor (MAOI). Phenelzine 15 mg twice daily was prescribed. After three days there was a small but encouraging early improvement and so the dose of phenelzine was increased to 15 mg three times daily.

After another two weeks there was no further improvement. TF continued to experience occasional severe panic attacks every three to four days with attacks of lesser severity intervening. His speech remained rapid and garbled and he continued to look tense. He still tended to avoid stressful situations.

The decision was made to reduce the diazepam and to introduce sodium valproate at a dose of 200 mg three times daily. After a week TF was subjectively improved. His panic attacks reduced in both severity and frequency. During the following week he continued to make good progress and was discharged.

It was decided that he should continue to attend the hospital three times a week as a day patient and undergo cognitive behavioural therapy (CBT). He would take the medication as prescribed with a continued gradual reduction of the diazepam.

Questions

1. What pharmacological options are available for the treatment of panic disorder? Briefly outline the differences between them.
2. What is the likely mechanism of action of these drugs?
3. Comment on the drug therapy used in this case.
4. Comment on the abrupt discontinuation of sertraline in this case.

Answers

1. What pharmacological treatment options are available for the treatment of panic disorder? Briefly outline the differences between them.

Panic disorder is a serious but common disorder affecting 1% of the population. Comorbidity with depression may be as high as 40%. Selective serotonin reuptake inhibitors (SSRIs) are now considered to be first-line therapy (Wade, 1999). However, only short-term benefit is to be gained from drug treatment alone. Relapse rates are high within months of stopping medication, so long-term treatment or a combination of medication with psychological therapy may be necessary.

Panic attacks usually provoke avoidance behaviour. The optimum strategy would be to suppress the symptoms of panic pharmacologically and then to modify behaviour and cognition with cognitive behavioural therapy. There is increasing evidence for the efficacy of cognitive behavioural therapy in panic disorder (Sharp et al, 1996; Busch, 1999).

Tricyclic antidepressants (TCAs), MAOIs and SSRIs, as well as benzodiazepines have all been shown to be effective pharmacological treatments for panic disorder although their spectrum of activity is different (Liebowitz, 1989). It has long been known that benzodiazepines block anticipatory anxiety, whereas antidepressants may prevent panic attacks but, at least initially, not anticipatory anxiety (Klein, 1964). Diazepam, chlordiazepoxide, alprazolam and clonazepam have all been used to provide short-term relief

from symptoms until antidepressants have time to exert their effects (Liebowitz, 1989).

Benzodiazepines are usually effective for the first week or more, but tolerability invariably develops. A worsening of symptoms can occur on withdrawal of treatment and this can lead to continuation of therapy with ensuing longer term problems. The short-acting benzodiazepine alprazolam has been tentatively shown to be the quickest, most effective treatment, with clonazepam also showing some efficacy (Cross National Collaborative Panic Study, 1992).

Antidepressants can take from four to six weeks to show maximum efficacy. Some patients require treatment for as long as 12 weeks before a treatment effect is seen (Wade, 1999), both SSRIs and TCAs can produce an increase in anxiety symptoms during the first weeks of treatment, which may lead to poor compliance. It is important to start treatment with low doses (e.g. imipramine 10–25 mg daily or paroxetine 10 mg daily) and increase slowly to minimize side-effects (Aronson, 1987). Tolerance does not develop to their beneficial effects and they do not produce dependence. The TCAs and MAOIs do, of course, have some troublesome side-effects, adverse reactions and potential interactions. In particular, the MAOIs can give rise to serious reactions with tyramine-containing foods. Although the reversible MAOI-A moclobemide is relatively free of these problems, it has been found, in a randomized controlled trial, to be no more effective than placebo in the short-term (eight weeks) treatment of panic disorder (Loerch et al, 1999). This same study found cognitive behavioural therapy (CBT) to be superior to placebo, with the combination of moclobemide and CBT being no more effective than CBT alone. Although this study was small, and probably lacked the power to detect moderate treatment effects, its findings do not support the use of moclobemide in the treatment of panic.

Of the TCAs, imipramine and clomipramine seem to be the most effective, with clomipramine being superior (Modigh et al, 1992). Controlled studies of the SSRIs show that paroxetine (Oehrberg et al, 1995; Ballenger et al, 1998), citalopram (Wade et al, 1997), fluoxetine (Michelson et al, 1999) and fluvoxamine (Hoehn-Saric et al, 1993) are all effective; although, to date, only

paroxetine and citalopram have been licensed for use in panic disorder. Some benefit has also been demonstrated with the MAOI phenelzine, although this is an unlicensed use for this drug.

A meta-analysis that included data from over 2000 patients concluded that SSRIs are more effective than imipramine or alprazolam in the treatment of panic (Boyer, 1995).

Despite initial claims to the contary, (Gastfriend and Rosenbaum, 1989) buspirone, a partial agonist at $5HT_{1A}$ receptors and chemically unrelated to any other anxiolytic, would seem to be ineffective in panic disorder, even with higher doses of the order of 60 mg daily (Sheehan et al, 1993).

The evidence for the efficacy of beta-adrenergic blocking agents in panic disorder is equivocal. Some workers have shown a combination of propranolol and a benzodiazepine to be beneficial while others have suggested that it is no better then placebo in this condition (Bailly, 1996). Nevertheless, there seems to be little doubt that this group of drugs has a significant effect on the somatic symptoms of anxiety. In particular, it has been shown that propranolol is of value in the treatment of hyperventilation (Suzman, 1971). They are not, however, without side-effects - fatigue and sexual dysfunction being commonly reported (Kostis, 1990).

Although unlicensed for this indication, there is some evidence of the efficacy of sodium valproate in the treatment of panic disorder (Woodmen and Noyes, 1994). Double-blind studies are still required for further verification of these findings.

One interesting double-blind, placebo-controlled, crossover trial found inositol (an isomer of glucose) to be effective in the treatment of panic disorder. Efficacy was particularly high in the subset of patients who experienced 10 or more panic attacks per week at baseline (Benjamin et al, 1995).

2. What is the likely mechanism of action of these drugs?

Central noradrenergic, serotonin, dopaminergic and GABA transmission systems have all been implicated in the aetiology of anxiety states. The benzodiazepines are thought to exert their action on the GABA receptor, mimicking the action of the inhibitory transmitter gamma-aminobutyric acid (Nutt, 1992). Similarly, sodium valproate appears to act as a GABA agonist (Roy-Burne et al, 1989).

It has been postulated that the SSRIs and clomipramine exert their anxiolytic effects via the serotonin system by increasing the overall level of central serotonergic transmission by inhibiting serotonin reuptake and by a direct desensitizing effect on pre- and post-synaptic inhibitory $5HT_{1A}$ receptors (Cowen, 1997). It is unclear, however whether panic disorder is actually mediated through serotonin excess or deficit in specific areas of the brain (Bell and Nutt, 1998).

Noradrenergic antidepressants such as imipramine may exert their anti-panic effect via presynaptic adrenergic $alpha_2$-autoreceptors (interfering with the negative feedback mechanism) (Heninger and Charney, 1988), although noradrenaline itself is also implicated in panic disorder, at least in a subset of patients (Bell and Nutt, 1998). Adrenergic $alpha_2$-receptors are also found on presynaptic serotonin neurones.

Whilst the beta-blockers predominantly affect the peripheral somatic symptoms of anxiety, it is thought possible that another important mechanism of action of the more lipophylic compounds is an interaction with central 5HT receptors along with beta-adrenergic blockade in the brain stem (Bailly, 1996).

Inositol is required for the functioning of the phosphatidyl-inositol cycle, a second messenger system used by some serotonergic and adrenergic pathways (Benjamin et al, 1995).

3. Comment on the drug therapy used in this case.

The SSRI sertraline is perhaps not the most effective of this group of antidepressants in reducing the symptoms of panic disorder, although it is licensed for the treatment of depression accompanied by anxiety. A higher dose of sertraline, to a maximum of 200 mg daily, could have been tried before the drug was discontinued. Of the SSRIs, it perhaps would have been more appropriate to try paroxetine or citalopram, since there is better evidence for their efficacy in panic disorder. Similarly, the dose of phenelzine could have been titrated upwards, side-effects permitting, to a maximum of 105 mg daily. In addition to this, up to 1000 mg daily of valproate has been successful in eliminating panic attacks with blood levels of the order of 77 mg/l being achieved (Roy-Burne et al, 1989). Twice daily dosage of valproate is preferred. The washout period between discontinuing sertraline and prescribing phenelzine was too

short, placing TF at risk of developing serotonin syndrome or significant side-effects.

Whilst TF eventually made good progress, more benefit may have been derived earlier if somewhat higher doses of the drugs prescribed had been tried before the treatment plan was changed.

With regard to gradual reduction of the daily dose of diazepam, it would have been advisable to have proceeded cautiously in view of the severity of TF's symptoms. The general recommendation would be a reduction of 2–2.5 mg of diazepam per fortnight. An exacerbation of symptoms may be seen if the reduction is carried out more quickly than this. TF is likely to require treatment with medication in the medium to long term. Patients who responded to a 10-week trial of fluoxetine and were then randomized to continue fluoxetine, or switch to placebo, fared significantly worse if active treatment was not continued (Michelson et al, 1999). Treatment guidelines recommend that 12–18 months should be the minimum treatment period and that the relapse rate, even at this point, is likely to be high (APA, 1998).

4. Comment on the abrupt discontinuation of sertraline in this case.

Abrupt discontinuation of SSRIs can lead to a withdrawal syndrome characterized by electric shock sensations, dizziness, lethargy, paraesthesia, nausea, vivid dreams, irritability and lowered mood. This may complicate management if unrecognized. The incidence of such symptoms occurring upon the abrupt discontinuation of sertraline is said to be lower than with some other members of this group by compounds (Coupland et al, 1996).

Key points

- The optimal treatment strategy for panic disorder is to suppress the symptoms of panic pharmacologically and then modify behaviour and cognition with cognitive behavioural therapy.
- Benzodiazepines offer relief in the short term.
- TCAs, some MAOIs and SSRIs may all be effective in panic disorder but can take four to six weeks to exert their full effect.
- Buspirone is ineffective in panic disorder.
- Propranolol and sodium valproate may be useful in some circumstances.

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17

Obsessive–compulsive disorder

Diane Booth

MM is a 26-year-old man with a 12-year history of obsessive-compulsive disorder (OCD) presenting as obsessional thoughts and rituals. These are usually well controlled but have become both intrusive and disabling following a recent move to a new high-profile job and a change of address.

MM's illness has a predominant pattern of obsessional thoughts concerning things or people he feels are unpleasant or evil, which he 'neutralizes' with symbolic and repetitive actions (usually in multiples of three).

For the last 18 months MM has been successfully treated with cognitive behavioural therapy (CBT) and clomipramine 175 mg daily. Three months ago, withdrawal of treatment was attempted but, after two months, symptoms re-emerged and fluoxetine 20 mg daily was initiated, with the intention of increasing the dose to 60 mg daily.

Unfortunately, MM did not tolerate fluoxetine and discontinued treatment because of sexual dysfunction before the target dose was reached. His OCD has worsened and he has become depressed and withdrawn.

Questions

1. Discuss the rationale behind MM's initial treatment.
2. Comment on the principles for the long-term treatment for MM.
3. What other treatment options are available and what is the rationale behind their use?

Answers

1. Discuss the rationale behind MM's initial treatment.

OCD is characterized by obsessions (persistent ideas and thoughts) and compulsions (repetitive behaviours and mental acts often performed in response to obsessions) which initially develop as a method of diverting stress and anxiety. Whilst many people realize their thoughts and actions are irrational and excessive, they often feel unable to control them. Treatment usually consists of medication, CBT, or a combination of the two.

MM's history is somewhat typical of the usual picture of OCD: the onset of the disorder is often in adolescence and complete recovery rare. Suffered by approximately 2% of the adult population and up to 4% of adolescents, OCD is more common in women. It often occurs alongside other disorders – most notably depression, but often tic disorders, social phobias, schizophrenia, bipolar disorders and attention deficit hyperactivity disorder (ADHD) (Weissman et al, 1994).

Individuals developing OCD later in life have a better prognosis (independent of duration of illness). The diagnosis of a concomitant schizotypal personality disorder predicts a poor drug response (Ravizza, 1998).

Both pharmacological and psychotherapeutic treatments have

been found to be effective, particularly in combination, but, frequently, patient preference will determine which treatment strategy is adopted (Abramowitz, 1997).

CBT, used either alone or in combination with a serotonergic antidepressant, is the most appropriate first-line treatment (March et al, 1997). CBT usually consists of exposure therapy coupled with response and ritual therapy, e.g. a patient with contamination worries must not only touch potentially dirty things but must refrain from ritualized washing until their anxiety diminishes. Cognitive therapy addresses exaggerated perceptions and feelings of responsibility. Although it has been estimated that between 80 and 90% of patients will respond to CBT (Abramowitz, 1997), OCD symptoms are usually reduced rather than eliminated and may remain disabling.

In milder OCD, CBT alone is the treatment of choice but, as the severity of the illness increases, CBT is more likely to be effective in combination with a suitable drug treatment (March et al, 1997). OCD responds almost selectively to drugs that inhibit the synaptic reuptake of serotonin (Goodman et al, 1990), primarily selective serotonin reuptake inhibitors (SSRIs) and clomipramine. Currently, in the UK, only five drugs are licensed for the treatment of OCD - fluoxetine, fluvoxamine, sertraline, paroxetine and clomipramine. Clomipramine is considered the gold standard for treatment of OCD, although its use has declined as newer agents with less severe adverse effects and lower incidence of lethality in overdose have become available. There are few trials available directly comparing the efficacy of SSRIs and clomipramine. Limited evidence points to clomipramine being slightly more effective overall (Greist et al, 1995).

The side-effect profile of each drug is important when initiating treatment. Whilst SSRIs offer a less anticholinergic side-effect profile, they may be associated with a greater incidence of headache, nausea, insomnia and agitation. In a patient considered a suicide risk, clomipramine would not be considered a suitable treatment choice because it is cardiotoxic in overdose.

The optimal treatment dose is the minimum dose that will achieve full therapeutic effect whilst minimizing

side-effects. Traditionally, high doses of both clomipramine and the SSRIs have been used both in trials and in practice, e.g. clomipramine up to 275 mg daily, fluoxetine up to 80 mg daily, paroxetine up to 60 mg daily, sertraline up to 200 mg daily, fluvoxamine up to 300 mg daily and citalopram up to 60 mg daily (March et al, 1997).

The dose should be increased slowly in order to minimize dose-related side-effects and to provide an opportunity for selecting the minimum effective dose. There is some evidence to suggest that standard antidepressant doses (rather than higher OCD doses) may be effective, particularly for long-term treatment. As always, when using high doses of clomipramine, regular ECG monitoring is advised and, when there is potential for drug interaction, blood level monitoring of clomipramine may be recommended.

A trial of at least 12 weeks is required before response to treatment can be assessed. A minor response may be enough to warrant a continued trial period, as patients who have had some initial response may continue to improve for several months (Greist et al, 1995).

2. Comment on the principles for the long-term treatment for MM.

Following the attempted drug withdrawal of clomipramine, MM suffered from re-emergence of symptoms. This is not unexpected, as the few studies available on the long-term treatment of OCD suggest that treatment must be continued indefinitely for patients to remain symptom free. Studies with both SSRIs and clomipramine over periods of up to two years indicate that the risk of relapse without medication is about 80%, whereas in those patients continuing with treatment, the risk of relapse is only 25–40% (Greist et al, 1995; Ravizza et al, 1996).

Maintenance treatment of OCD should be continued for at least one to two years and discontinued only if patients are stable. In patients who have had more than two relapses, long-term prophylactic treatment must be considered (March et al, 1997). Dose reduction may be considered for long-term treatment but should not be attempted during the first year (Ravizza et al, 1998). However, long-term maintenance treatment may be continued at 50% of the dose used in an acute episode with no significant reduction in efficacy. This may improve

both compliance and tolerability for the patient (Pato et al, 1990; Ravizza et al, 1996).

Discontinuation of medication may be attempted if the patient has been clinically stable for at least one year. Discontinuation should be over a period of months in order to reduce the likelihood of relapse and symptom recurrence. As a guide, the dose should be reduced by 25% every two months. Patients should be warned to look out for early signs of relapse, at which point the drug may be reinstated with the same level of improvement as before (March et al, 1997).

Patients receiving an SSRI may be more at risk of relapse than those receiving clomipramine if the drug is discontinued abruptly (fluoxetine is the exception because of its long half-life), particularly in the first two months following discontinuation (Ravizza et al, 1998). Following the reinstatement of medication at the same doses that had been used previously, response to treatment may occur within two to four months (Ravizza et al, 1998).

During trials, drop-out rates due to side-effects from clomipramine are consistently higher than for the SSRIs (Pato et al, 1990). Because of the requirement for long-term treatment and the relatively high doses that are often required, side-effects can be problematic and lead to non-adherence to treatment. Drug holidays have been suggested to minimize some dose-related side-effects such as sexual dysfunction, but there is little objective data to support this recommendation (Fineberg, 1999). Patients should be advised that the majority of side-effects occur in the first two months of treatment and that tolerance to many side-effects may develop. However, problems such as sexual dysfunction, SSRI-induced movement disorders and the anticholinergic side-effects of clomipramine may be intolerable, and thus an alternative treatment strategy should be sought.

3. What other treatment options are available, and what is the rationale behind their use?

Whilst there is no direct evidence-based guideline that dictates the management of refractory illness with respect to drug treatment, there is agreement surrounding general treatment principles. Following a period of adequate treatment (adequate doses for at least a 12-week trial period) with at least three SSRIs

(including clomipramine), plus CBT augmentation strategies may be considered. The nature and severity of any co-morbid disorder will often determine treatment choice (Dominguez and Mestre, 1994).

The rationale behind augmentation strategies is to increase the serotonergic activity/concentrations in the synapse. This may be achieved by increasing serotonin precursors, increasing the release of serotonin from presynaptic neurones, or preventing reuptake or metabolism.

Desmethylclomipramine (DCMI) is the major active metabolite of clomipramine and has both serotonin and norepinephrine reuptake-inhibiting effects. Intravenous (IV) administration of clomipramine leads to an increased clomipramine/DCMI ratio by avoiding first-pass metabolism. IV clomipramine was first reported to be successful in treating obsessive symptoms in 1967. In a double-blind placebo-controlled trial of IV versus oral pulse loading, after four and a half days, six out of seven patients treated with IV clomipramine were responders, compared with one out of eight treated with oral clomipramine (Koran et al, 1997). IV loading may then be followed by a higher than usual oral dose of clomipramine (Warneke, 1989).

Exceeding the recommended daily dose of an SSRI may improve a patient's response. Doses as high as 300 mg daily of sertraline may be necessary in some patients, but evidence for this remains inconclusive (Byerly et al, 1996).

Other antidepressants have been used as monotherapy or as adjuncts with some success. Monoamine oxidase inhibitors (MAOIs), which block the breakdown of 5-HT, norepinephrine and dopamine, have anecdotally proved effective for patients resistant to SSRI treatment and those with co-morbid anxiety disorders (Dominguez and Mestre, 1994). Phenelzine in doses of 45–90 mg daily has been used with some success (Vallejo et al, 1992). However, the most recent controlled trial found fluoxetine to be more effective than phenelzine for controlling OCD symptoms (Jenrike et al, 1997). When using MAOIs, an appropriate washout period before drug initiation and a two week washout after discontinuation must be enforced in order to avoid potentially serious drug interactions and side-effects.

Trazodone and nefazodone both act as SSRIs and, whilst not usually effective

as monotherapy, may be useful as adjunct treatment. Low doses (25–100 mg daily) may, perhaps because of CYP450 enzyme interactions, increase SSRI blood levels, thus potentiating their actions at lower doses. Problematic side-effects such as anxiety and insomnia may be improved by the addition of these agents (Dominguez and Mestre, 1994).

Use of adjunctive agents such as lithium, tryptophan, pindolol and buspirone, whilst successful in anecdotal reports, has not yet been supported by more rigorous studies. These agents may be more useful for patients with co-morbid illness (Dominguez and Mestre, 1994).

Venlafaxine is a serotonin and norepinephrine reuptake blocker similar to clomipramine, but without the anticholinergic and antihistaminicergic blockade and associated side-effects. Patients intolerant of, or resistant to treatment with SSRIs and clomipramine may benefit from venlafaxine. Relatively low doses of 150 mg daily may be effective (Ananth et al, 1995). There are no randomized controlled trials.

More promisingly, clonazepam 1–3 mg daily may be effective both as monotherapy and as an augmentation strategy. Six-week trials have suggested that clonazepam may be as effective as clomipramine. Clonazepam in combination with an SSRI may be particularly useful for partial responders to first-line therapies. The maximum response to clonazepam tends to be seen in the first few weeks of treatment, whilst the response to an SSRI continues to improve for much longer. This suggests that clonazepam is exerting an anxiolytic rather than specific anti-OCD effect. It should be noted that whilst clonazepam and clomipramine are equally effective after six weeks, after three months clomipramine is superior. The additional relief of anxiety provided by clonazepam may be useful, supporting both pharmacological and other treatment strategies (Hewlett et al, 1992).

Addition of a low-dose antipsychotic (e.g. haloperidol 0.5 mg) or an atypical antipsychotic (e.g. risperidone 1 mg) to an existing antidepressant treatment may be helpful for those patients with co-morbid tics or Tourette's syndrome. However, there are reports of some of the newer atypical agents worsening OCD, particularly when used as monotherapy (McDougle et al, 1995). Antipsychotics that block postsynaptic 5-HT_2 receptors have been associated

with the development of de novo OCD symptoms. In line with this observation, clozapine has been shown to be ineffective in OCD and may even have the potential for exacerbating symptoms (McDougle, 1997).

Optimistic reports of the anti-androgenic drug cyproterone acetate having some therapeutic effect in OCD have not been confirmed. Flutamide (an androgen-receptor antagonist) has also been shown to be ineffective (Altemus et al, 1999).

Other putative treatments for severely ill patients include electroconvulsive therapy, repetitive transcranial magnetic stimulation and neurosurgery (Goodman, 1999).

Key points

- The treatment of OCD is difficult and not always effective.
- CBT with a serotonin reuptake inhibitor is the mainstay of treatment.
- Antidepressant pharmacotherapy at high doses for at least a 12-week trial is necessary.
- Second-line treatments may be effective but are poorly supported by published trials.

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18

Mania

Peter Pratt

MP, a 54-year-old lady, was admitted to an acute psychiatric ward after being found outside her house earlier in the day, dressed in her night attire. A member of the public had complained that MP had become verbally aggressive when she refused to join MP in saving the world.

It was difficult to obtain a full history from MP as her speech was rapid and made little sense. She often made reference to being God and her need to save the world. MP would often break into song, 'Oh what a beautiful morning', in the middle of a sentence.

MP normally lived on her own and had no recent contact with her family. She had one daughter from a previous marriage which had ended 15 years previously. MP had not worked since her father's newsagents business closed in the 1970s. There did not appear to be an obvious precipitant to this episode.

MP had records of two previous admissions, two and five years ago. Her records indicate she had received lithium, carbamazepine, haloperidol, droperidol and chlorpromazine at various times during these admissions, often in combination. She had not recently been prescribed any medication and a urine screen confirmed she had not been taking any illicit drugs.

On the ward MP was sexually disinhibited, asking other patients to have sex with her and produce God's children. On occasions she became verbally aggressive, particularly when other patients asked her to leave them alone.

Following assessment MP was diagnosed as having an episode of mania.

Questions

1. Discuss the pharmacological treatment options for an episode of mania.
2. Formulate a drug treatment plan for MP.

Answers

1. Discuss the pharmacological treatment options for an episode of mania.

Any physical basis for MP's symptoms should be identified and managed appropriately. Such causes would include cerebral disorders, infections and drug or alcohol misuse. Many prescribed drugs have been reported to induce mania, particularly antidepressants and steroids.

The choice of treatment for mania includes lithium, valproate, benzodiazepines, traditional antipsychotics, carbamazepine or, in resistant cases, combinations of these drugs (Licht, 1998). Electroconvulsive therapy (ECT) also has a role. Other treatment options include atypical antipsychotics, other anticonvulsants, calcium-channel blockers and beta blockers (Dubovsky and Buzan, 1995).

In the acute manic phase, prompt treatment is essential. The patient may be at physical risk through exhaustion

and their actions may lead to financial or social disaster for themselves and their family. Reckless behaviour may result in loss of employment or criminal conviction. Loss of life or injury to the patient or others may occur if the patient continues with potentially dangerous activities such as driving. Increased sexual activity may lead to pregnancy, sexually transmitted disease and, in some cases, may make it difficult for the patient to return to their friends or family. Suicidal thoughts are uncommon in pure mania but may occur in >50% of cases when symptoms of both mania and depression occur nearly every day (a mixed-mood state) (Dilsaver et al, 1994). If episodes recur, then longer term prophylactic treatment should be considered.

Moncrieff (1997) and Cookson (1997) have debated the relative pros and cons of treatment with lithium. These two reviews contained few common references and could be criticized as being biased, albeit opposing, views, where the authors selectively searched the literature in order to locate references which were in line with their own opinions. Despite the confusion caused by the two opposing views presented in these reviews and the paucity of good quality randomized controlled trials, lithium is still considered by many clinicians to be a first-line prophylactic treatment of bipolar disorder. Initiation of long-term treatment should not be considered lightly as premature abrupt discontinuation is associated with a high relapse rate (Suppes et al, 1991; Goodwin, 1994). This should be discussed with the patient before prescribing lithium and a minimum duration of treatment of at least three years agreed.

Several recent reviews (Licht, 1998; Poolsup et al, 2000) confirm the unique place of lithium in both the acute and prophylactic management of mania. However, the body of evidence supporting the use of alternatives continues to grow. Valproate (as divalproex or valproate semisodium) is frequently advocated as a first-line alternative to lithium, particularly in the USA (Sachs et al, 2000).

To be an effective antimanic agent, lithium needs to be given in sufficient dosage to produce 12-hour lithium levels of around 1.0–1.2 mmol/l. Even then, worthwhile response may be delayed for up to 10 days. The risk of lithium toxicity when treating an

episode of mania is significant. There can be great variability in fluid intake and physical exertion, and physical monitoring may be difficult.

Within the UK at least, it is common practice to use alternatives to lithium in the management of severe mania and those with psychotic symptoms (Peet and Pratt, 1993). In those with psychotic symptoms, concomitant treatment with antipsychotics is the norm (Chou et al, 1996; Gelenberg and Hopkins, 1996). Indeed, antipsychotics are frequently used even when psychotic symptoms do not predominate. Antipsychotics are considered to be effective in the treatment of mania, but again randomized clinical trials are few. The small numbers of studies account for the observation that different authors give completely different views. Moncrieff (1997) opined that the majority of studies demonstrate the superiority of antipsychotics over lithium, whereas Bowden (1996) suggests that from randomized comparisons, antipsychotics are consistently shown to be less effective than lithium. There is increasing evidence to support the use of atypical neuroleptics in the treatment of mania (Worrel et al, 2000).

The impression of most clinicians is that antipsychotics are effective in mania and that they appear to have a more rapid effect than lithium (Chou, 1991). Chlorpromazine is the antipsychotic that has been most frequently studied but trials involving other antipsychotics appear to show similar benefits, leading Chou (1991) to conclude that there is little difference in antimanic response between the traditional antipsychotics, particularly in controlling hyperactivity. Nevertheless, the use of flupenthixol may be unwise, in view of the manufacturer's SPC (summary of product characteristics). This includes advice that this drug is not suitable for agitated or excited patients.

In routine clinical practice haloperidol is often cited as the antipsychotic of choice. Droperidol is no longer used because of the risk of cardiac arrhythmias. Where medication must be given parentally, zuclopenthixol acetate (Clopixol Acuphase) may offer practical advantages when repeated intramuscular (IM) injections might otherwise be necessary.

There is an increasing trend towards using lower doses of traditional antipsychotic drugs like haloperidol. For example, there is limited, but

convincing, evidence that there is nothing to be gained by increasing the dose of haloperidol to above 10 mg daily in the management of mania (Rifkin et al, 1994). However, haloperidol doses lower than 10 mg daily are said to be too low to be effective as monotherapy (Chou et al, 1999). If additional sedation is required, adjunctive treatment with a benzodiazepine would appear less hazardous than increasing the doses of the antipsychotic. The most likely therapeutic benefit from higher doses of antipsychotics is enhanced sedation. This may be misinterpreted as improved antipsychotic effect. Higher doses will invariably be associated with an increased incidence of extrapyramidal side effects (EPSEs). This, too, may be considered therapeutic: drug-induced akinesia effectively reduces the severity of behaviour associated with mania.

The atypical neuroleptics olanzapine (Tohen et al, 2000), clozapine (Frye et al, 1998) and risperidone (Segal et al, 1998) have all been shown to reduce the symptoms of mania. Quetiapine may also be effective (Zarate et al, 2000). Concern about the possible increased risks of tardive dyskinesia in patients with bipolar illness will undoubtedly fuel the interests in the use of these agents.

In addition to the established antimanic effect of valproate, limited evidence suggests that it may be more effective as a prophylaxis against manic episodes than depressive episodes (Lennkh and Simhandl, 2000). Valproate loading may also be effective in mania (Hirschfeld et al, 1999). The use of valproate and other anticonvulsants is covered in Chapter 19.

Limited evidence supports the use of carbamazepine as monotherapy (Vasudev et al, 2000). However, the drug is not licensed for this purpose in the UK. Various reviews, including those incorporating open studies and case reports, suggest a response rate of around 60% in mania (Elphick, 1989; Chou, 1991). Subgroups of manic patients likely to respond to carbamazepine have not been clearly identified. Empirically, there appears to be support for using carbamazepine in those patients refractory to lithium, typically those with rapid cycling bipolar disorder.

Response to carbamazepine is likely to occur from around five days to one month after initiation of treatment.

Carbamazepine dosage should be titrated slowly from 200 mg once or twice daily (increased every five days in the early part of treatment) until either the patient responds, or is unable to tolerate further increases. Carbamazepine plasma levels do not appear to correlate with response, but may also help to predict toxicity. Inadequate dose could explain an apparent lack of response, if steady state plasma levels <7 mg/l are achieved (Taylor and Duncan, 1997). Carbamazepine should only be considered for the treatment of an episode of mania if other treatment options are either ineffective or impracticable. Modified release preparations are usually better tolerated.

Some limited evidence exists to support the use of the higher potency benzodiazepines, clonazepam and lorazepam as anti manic agents in their own right (Santos and Morton, 1989; Bottai et al, 1995). A case can be made for benzodiazepines both enhancing the effects of antipsychotic drugs and having antipsychotic effects of their own (Wolkowitz et al, 1991).

In routine clinical practice the major role for benzodiazepines appears to be in combination with antipsychotics or lithium. The aim is to produce a rapid calming effect without resorting to large doses of antipsychotics, or to produce rapid control of psychomotor agitation until the antimanic effects of the other treatment become apparent. Lorazepam and diazepam are available as parenteral as well as oral forms. Diazepam should not be given intramuscularly as absorption is unpredictable. Treatment with benzodiazepines should be considered a short-term strategy as tolerance and dependence are likely to occur with longer term treatment.

The desire to avoid polypharmacy should not preclude the appropriate use of combinations of drugs. Neuroleptics and/or benzodiazepines can be useful adjuncts to non-sedating treatments such as lithium, carbamazepine or valproate. In particular, combination treatments should be considered for all those unresponsive to monotherapy (Gouliaev et al, 1996).

2. Formulate a drug treatment plan for MP.

Pharmacological treatment is important. MP is clearly at risk of being exploited or harmed by others. She may assault other patients and appears to have little insight into her condition.

As far as is possible, MP should be assessed to ensure that she is physically well, with no apparent contraindications to drug treatment. Possible precipitating causes such as drugs of abuse, or prescribed drugs such as steroids, should be excluded. MP's previous episodes may provide useful information on the effect of medication and the time course for response. Target symptoms should be documented.

As MP's mania presents with psychotic symptoms, initial treatment should be with an antipsychotic. A benzodiazepine should be used to provide additional sedation. Treatment should start with haloperidol 5 mg twice daily and lorazepam 2 mg twice daily. Other antipsychotics such as chlorpromazine could be considered as alternatives. Written and verbal explanation of the treatment should be given to MP.

If MP does not accept oral medication, consideration should be given to administering medication against her wishes under the Mental Health Act. Clopixol Acuphase may be used instead of repeated IM doses of haloperidol.

If symptoms of disinhibition have not improved within seven days then consideration should be given to increasing the dose of benzodiazepine and antipsychotic. MP's delusional belief that she is God and needs to save the world may take several weeks to respond.

In recovery, the duration of sleep may be a good indicator for judging the rate of benzodiazepine reduction. Haloperidol should not be discontinued prematurely.

As this is MP's third episode of mania within five years, consideration should be given to prescribing prophylactic medication. Lithium is the treatment of choice. Time must be spent in helping MP understand the implications of long-term treatment with lithium. Some clinicians believe that lithium should not be prescribed unless MP agrees to take the drug for several years (preferably at least three years).

Key points

- Antipsychotics and benzodiazepines in combination are the drugs most frequently prescribed to treat an episode of acute mania.

- Haloperidol is probably the antipsychotic of choice. In time, accumulated evidence may support the use of atypical antipsychotics.
- The non-specific sedative effects of antipsychotics should not be confused with their antipsychotic action.
- Benzodiazepines usefully augment the efficacy of antipsychotics.
- Valproate semisodium may be considered as a first-line alternative. Lithium, ECT, other anticonvulsants and calcium-channel blockers are other alternatives.
- The risk of manic relapse after discontinuation of lithium is high. This should be considered before prescribing lithium to treat an episode of mania.

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19

Bipolar disorder: unlicensed treatments

Peter Pratt

AS, a 45-year-old unemployed baker, had been admitted to an acute psychiatric ward some three months previously following a deterioration in his relationship with his partner of 10 years.

During this admission, ward staff noted frequent episodes of sexual disinhibition. At other times he appeared weepy and apologetic. Occupational therapy staff reported his very short attention span and inability to concentrate. His sleep pattern varied considerably but he frequently reported little need for sleep.

AS first presented to the psychiatric services six years ago following referral by his GP. He presented with poor appetite and sleep disturbance, was very weepy, felt unable to cope and could not face going to work. He felt his workmates were trying to get him sacked by putting insects or glass in the bread he baked.

These symptoms were well controlled by fluoxetine 20 mg daily and trifluoperazine 10 mg daily. A year later, AS was admitted to an acute psychiatric ward: his partner had become unhappy at his increasingly frequent and bizarre sexual demands. At the time he also believed she had become a prostitute and would be able to access all the other prostitutes in the city. A diagnosis of mania was made and AS was successfully treated with lithium carbonate.

Over the next four years AS had five further psychiatric admissions, one for a depressive episode and four due to mania. Both AS and his partner confirmed that he regularly took lithium and blood levels confirmed a reasonably steady 12-hour level of around 0.6–0.8 mmol/l. Twelve months before his current admission lithium was discontinued and carbamazepine started in an attempt to prevent further episodes.

Extensive medical and neurobiological investigations have uncovered no abnormalities. AS does not normally drink alcohol and has not misused drugs for at least 20 years. In the past he had taken various illicit substances, particularly magic mushrooms and anabolic steroids.

AS's current diagnosis is bipolar affective disorder, manic episode. He is treated with haloperidol 9 mg daily (occasionally up to 15 mg), procyclidine 5 mg twice daily, temazepam up to 20 mg at night and carbamazepine 1600 mg daily (as 600, 400 and 600 mg). There are no grounds to suspect non-compliance with medication. Serum carbamazepine levels are between 10 and 12 mg/l. In retrospect, AS feels that lithium did not help at all; it just reduced his sex drive.

In view of his apparent non-response to lithium or carbamazepine, AS is asked to consider taking sodium valproate – an unlicensed treatment.

Questions

1. What is meant by an unlicensed treatment?
2. What are the implications for prescribers of using unlicensed treatment and in what framework should it be undertaken?
3. What are the pharmacological treatment options for AS?

Answers

1. What is meant by an unlicensed treatment?

In the UK, the Medicines Control Agency (MCA) is the main body that must be satisfied that a medicine is both safe and effective for its intended use. In order to reach this conclusion, the MCA will require a manufacturer to submit supporting data demonstrating the effects of the medicine. The MCA considers animal data (from preclinical studies), healthy volunteer data (usually phase I clinical studies) and patient data (usually phase II and III studies). Preclinical studies may employ animal models of human disease states and are also concerned with acute and chronic toxicity. Early clinical studies are concerned with determining the drug's clinical pharmacokinetics. Dose-finding studies follow, and then randomized, placebo-controlled, double-blind trials in patients. Many of the patients treated routinely in clinical practice are excluded from clinical trials, e.g. the elderly, those who have significant physical pathology, or those who cannot give informed consent.

If a manufacturer wants to extend the use of a licensed drug, similar supporting evidence for the intended new use must be provided to the MCA. If, then, the MCA is satisfied that a new medicine or a new use of an existing medicine is safe, effective and brings about overall benefit, then the licensing authority will grant a marketing authorization (previously known as a product licence). Health economic (cost effectiveness) data are not currently required by the MCA. The recently established National Institute for Clinical Excellence (NICE) is not part of the UK licensing process.

Following the formation of the European Medicines Evaluation Agency (EMEA) in 1995, the process of marketing authorization has been co-ordinated across the European Union. If a marketing authorization is granted in one country, it is expected that this would be recognized in other member states.

Any drug that has not been granted a marketing authorization is termed an unlicensed product. Also, the use of licensed medicines in conditions or dose schedules not included in their marketing authorization is officially unlicensed use (sometimes called 'off label').

Valproate semi-sodium (divalproex or Depakote) has a marketing authorization for the treatment of mania, but if used as prophylaxis for the management of bipolar disorder it would be considered an unlicensed treatment. Sodium valproate has a marketing authorization only for the treatment of epilepsy. All other uses are thus 'off label'.

2. What are the implications for prescribers of using unlicensed treatments and in what framework should it be undertaken?

Few people outside the licensing process will know the full details of a marketing authorization for a particular drug. From a practical point of view, the information required to prescribe within the marketing authorization will be contained within the medicine's summary of product characteristic (SPC).

The majority of SPCs are contained in the data sheet compendium published by the ABPI, also available on the internet (http://emc.vhn.net/professional/). (Manufacturers who are not members of ABPI will not have their SPC included in this text.)

If a drug is prescribed, there is an expectation that this is done knowingly, i.e. with an appreciation of information contained in the SPC. If no reference is made to the SPC it may be alleged that the prescribing was done negligently (Anon, 1992).

However, doctors may still reasonably prescribe unlicensed medicines or use medicines outside their marketing authorization. Warnings and special

precautions may be overridden. Advice may also be given to other prescribers to use a product in an unlicensed way. However, responsibility for both efficacy and toxicity may then lie entirely with the prescriber.

Drugs that have no marketing authorization for any indication must be obtained on a 'named-patient' basis, before they can be supplied to a patient. Such drugs are not routinely stocked in any pharmacy. Pharmaceutical manufacturers may supply a product for a 'named patient', but it is important to emphasize that it is the prescriber who bears all responsibility for its use.

The process of obtaining or extending the marketing authorization for a medicine is an expensive process. It may be uneconomic for a manufacturer to apply for an extension to cover a small-scale, specialist use of a product. This is why many drugs continue to have a narrow range of official indications, despite use in other conditions. This is commonly the case for many medicines used in children.

If called to justify the use of an unlicensed drug, a prescriber may find it helpful to refer to standard texts such as the British National Formulary (2001) if they support the use in practice, although such texts often mirror information contained in SPCs. Widely held clinical opinion as voiced in consensus statements, or Royal College guidelines, are another source of support.

As a general principle an unlicensed treatment should not be used in place of an effective and well-tolerated licensed treatment (the process of marketing authorization is in effect supporting the use of evidence-based pharmacotherapy). The use of an unlicensed product in place of a licensed one on purely economic grounds could initially be perceived as problematic. The 'art' of medicine, however, is complex and the more established the use of a drug is then the less likely any successful legal challenge would be.

In psychiatric practice there are often a significant number of patients who show a limited or partial response to existing treatments. Considering this, together with some of the disabling side-effects of many psychiatric drugs, the use of unlicensed treatments is understandable and often justifiable.

The prescriber should always document the reasons for prescribing in the clinical notes and seek to explain this to the patient. This is good practice, irrespective of whether the drug prescribed is licensed or not. In particularly risky circumstances, when the action of the prescriber would not be considered 'normal custom and practice', it may be wise to seek a second opinion.

An unlicensed treatment will not normally contain a patient information leaflet or, if used in an unlicensed way, may confuse the patient, as the leaflet may make no reference to their condition. The reasons for this should be explained to the patient.

3. What are the pharmacological treatment options for AS?

AS has been treated with 9–15 mg daily of haloperidol for the duration of his current admission. Depending on the route of administration, the licensed maximum daily dose for haloperidol is 15 mg orally (30 mg for treatment-resistant schizophrenia) or 18 mg parenterally. Normally, there appears little rationale for increasing the dose above 10 mg, at least in schizophrenia (Rifkin et al, 1994). The BNF suggests using doses of around 6–15 mg (BNF, 2001). Increasing the dose above 15 mg would normally be considered an unlicensed use. Despite widespread use in some areas, in anything other than exceptional cases, the use of antipsychotics in doses above the licensed maximum would not be supported by informed clinical opinion (Thompson, 1994).

Carbamazepine is licensed for use in epilepsy in daily doses of up to 2000 mg daily. In the prophylaxis of bipolar disorder 1600 mg is the maximum licensed daily dose. Little evidence exists to support the use of carbamazepine in doses above this. Simhandl et al (1993) found no difference in prophylactic efficacy in bipolar patients with low or high serum levels of carbamazepine. There appears no justification for exceeding the licensed dose in this case.

Valproate semisodium (as divalproex – an equimolar combination of sodium valproate and valproic acid) is licensed only for the treatment of acute mania associated with bipolar disorder. Despite widespread use throughout the USA, further work is required before the place of valproate in bipolar disorder can be defined (Lennkh and Simhandl, 2000).

The evidence supporting the use of valproate in bipolar affective disorder and schizoaffective disorder originates mostly from open studies that do not include a placebo arm. In both the treatment of mania and the prevention of manic relapse, the evidence, although limited, appears more robust (Silverstone and Romans, 1996; Ahmed and Morriss, 1997; Lenkh and Simhandl, 2000). In the treatment of mania the response rate appears to be similar to lithium, at around 50% (Bowden et al, 1994; Bowden, 1996). Data from a multicentre, double-blind study of 179 hospitalized manic patients suggests that those with depressive symptoms at baseline were less likely to respond to lithium than to divalproex (Swann et al, 1997). Although the overall response rate appeared similar, the authors suggest that lithium and divalproex may be effective in clinically and biologically distinct groups. These conclusions should be confirmed by further studies before they are considered definitive.

Debate continues over whether to use the licensed, expensive, form of valproate (Depakote) or the unlicensed, cheaper, forms (eg Epilim). There is no legal precedent to guide practice.

In view of AS's predominant manic symptoms and failure to respond to established licensed treatment, valproate preparations should be considered. In the short term, combination with haloperidol may also be necessary.

There is no consensus on dosage for prophylaxis. Ahmed and Morriss (1997) suggest treatment should be started at 250 mg two or three times daily and then increased by 250–500 mg every three days to a maximum dose of 60 mg/kg daily. The dose should be adjusted according to side-effects and response. There is no clear relationship between plasma level and response (Bowden, 1996). Patients who suffer from gastrointestinal side-effects with the conventional tablets may be switched to the slow-release form, which is usually better tolerated. A review by Taylor and Duncan (1997) concurs with others in advising that plasma levels >50 mg/l are required for a therapeutic response. Side-effects seem more common with levels above 100 mg/l.

If AS responds to valproate semisodium then long-term prophylaxis would be justified.

As neither sodium valproate (as Epilim) or valproate semisodium (as Depakote) are licensed for prophylaxis, some clinicians would consider switching to sodium valproate because of the considerable cost differences, others would advocate continued use of semisodium valproate. Modified release preparations of Epilim also have the advantage of less frequent (ie once daily) dosing.

Other drugs may also be considered. Double-blind placebo-controlled studies, open studies and case reports provide increasing evidence for the benefit of lamotrigine, both as monotherapy and in combination with other mood stabilizers (Freeman and Stoll 1998; Botts and Raskind, 1999; Calabrese et al, 1999).

Case reports and open studies support the use of gabapentin, topiramate, phenytoin and tiagabine (Maidment, 1999). This data should be considered preliminary and well-designed controlled trials are required. It is likely that anticonvulsant drugs will differ in efficacy. Preliminary observations suggest that lamotrigine may be useful in bipolar depression and topiramate in mania.

Benzodiazepines may have a role over and above any sedating or tranquillizing effect. Lorazepam is frequently used in mania as an adjunct to other treatments where its primary role is in reducing the need for additional doses of antipsychotic. Some published evidence also supports the use of clonazepam, although the small number of cases and use of drug combinations make it difficult to conclude that clonazepam has a specific antimanic effect. Chouinard et al (1983) found clonazepam to be as effective overall as lithium, but superior in controlling hyperactivity. There is no compelling evidence that would support the long-term use of benzodiazepine in bipolar disorder.

There is a reasonable theoretical base for using calcium-channel blocking agents in bipolar disorder. Elevated levels of calcium ions have been found in both platelets and lymphocytes of manic and depressed bipolar patients.

Of the calcium-channel blockers, verapamil is the best supported by double-blind, placebo-controlled studies, as well as open studies and case reports (Hollister and Trevino, 1999). The available evidence suggests that verapamil in doses around 240–480 mg is effective in the treatment of mania. Unlike valproate and carbamazepine,

verapamil may not be as effective in lithium-resistant cases. Overall, there are insufficient data to conclude that verapamil is as effective as lithium. Walton et al (1996) in their single-blind study of 40 manic patients found lithium to be a superior treatment.

The evidence supporting two other calcium-channel blockers, nifedipine and nimodipine, is limited. Given that these drugs may act at different binding sites in the brain, individual calcium antagonists may prove to have benefits over and above their 'class effects'. The prophylactic effect of calcium antagonists is yet to be determined. Adverse effects such as hypotension and constipation are often dose limiting, especially with verapamil.

Drug combinations may also be used. In an attempt to quantify the risks and benefits of drug combination in the treatment of bipolar disorder, Freeman and Stoll (1998) reviewed the published evidence and concluded that the safest and most effective mood stabilizer combinations were anticonvulsants, particularly sodium valproate, with lithium.

Many other unlicensed treatments have been tried in bipolar disorder (Lerer, 1985), but their use should only be considered under exceptional circumstances. Effective non-pharmacological strategies, such as ECT (electroconvulsive therapy) should not be discounted in favour of these obscure treatments. Several of the atypical antipsychotics, including clozapine (Frye et al, 1998), have also been used. None is specifically licensed, although the marketing authorization for risperidone is broad in that it covers the treatment of 'psychosis'. Acute mania with psychotic symptoms would be a licensed use but prophylaxis would not.

The absence of extrapyramidal problems should encourage further work in identifying the role of these agents in both the acute treatment and long-term prophylaxis of bipolar disorder.

Key points

- Satisfactory evidence of both safety and efficacy is required before a marketing authorization is issued.
- The marketing authorization process does not take account of cost effectiveness, but can be considered as evidence based.

- When a drug is prescribed for an unlicensed ('off label') use, the prescriber usually bears full responsibility for any adverse consequences.
- Prescribing 'off label' is often reasonable. Patients have a right to be informed of the potential risks and benefits of all medication prescribed for them.
- Support for prescribing in an 'off label' situation may be found in the BNF, or may take the form of widely held clinical opinion voiced in consensus statements.
- Valproate, in any form, is not licensed for long-term prophylaxis in bipolar disorder.

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20

Lithium prophylaxis, withdrawal and use in pregnancy

Stephen Bazire

NH, an intelligent, 35-year-old woman with a stable bipolar mood disorder has been prescribed lithium 600 mg at night for six years following two major hypomanic episodes. Since then, she has been stable for four years. NH had one depressive episode five years ago, during which she made an attempt to take her own life. NH has been married for three years and has been functioning well. She attended a routine outpatient appointment, where she announced that she had stopped taking her lithium three days ago as she would like to start a family. (Her GP had advised her that lithium was teratogenic.)

Questions

1. What are the main advantages for NH of continuing to take lithium?
2. What problems might be expected if lithium is stopped abruptly as with NH?
3. What problems might be anticipated when lithium is taken during pregnancy?

Answers

1. What are the main advantages for NH of continuing to take lithium?

Lithium is widely used for the treatment and prophylaxis of bipolar affective disorder, a practice supported by at least 10 major placebo-controlled trials of lithium [the most recent being Bowden et al (2000)]. Although many have methodological flaws (eg most used a lithium-withdrawal control group), their findings are considered reasonably conclusive. Prophylactic use of lithium can, with appropriate care and monitoring, be both effective and safe. Lithium must be taken regularly and monitored correctly, preferably at a lithium clinic (Kallner et al, 2000), and the risks and benefits of ongoing treatment must be regularly reviewed, with consideration to the clinical circumstances of each individual case.

The prophylactic efficacy of lithium is probably maintained over at least 10 years (Berghofer et al, 1996). Extensive data has also accumulated to suggest that long-term lithium treatment markedly reduces the excess mortality of people with recurrent affective disorders (Muller-Oerlinghausen et al, 1996) by reducing the high suicide rate (Baldessarini et al, 1999). Conversely, discontinuation of lithium prophylaxis has been shown to be associated with elevated rates of psychiatric hospitalization, greater use of emergency services (eg Johnson and McFarland, 1996) and a greater suicide rate (Baldessarini et al, 1999).

Refractoriness to lithium, despite adequate lithium levels, apparently induced by lithium discontinuation in previously lithium-responsive patients, has been reported many times (eg Bauer, 1994; Maj et al, 1995). There is, however, some dispute about this, largely because a well-designed study

that followed 86 patients over two lithium maintenance treatment periods (mean four years each) was unable to replicate these findings (Tondo et al, 1997). In this study it is of note that no difference in response rates was seen between the first and second treatment periods, irrespective of the gap between treatment periods or the rate of discontinuation of lithium after the first treatment period. This is particularly interesting, as it is thought that patients with bipolar disorder tend to have more frequent episodes as they get older.

Thus, the prevention of relapse, reduction of suicide risk and possible prevention of future refractoriness are suggested major advantages of continuing lithium for someone like NH, who has an established bipolar illness.

2. What problems might be expected if lithium is stopped abruptly as with NH?

Early relapse in bipolar illness following lithium discontinuation is well accepted. The risk of recurrence (predominantly of mania) in bipolar disorder may be up to 28 times higher in the first three months after stopping lithium than it is for those patients who continue to take lithium (Suppes et al, 1991). This recurrence rate may even exceed that of untreated bipolar illness.

Two studies have illustrated the danger of abrupt discontinuation. The first (Baldessarini et al, 1996) studied 161 people who had been taking lithium for an average of four years and who wanted to stop. One group stopped abruptly (over one to 14 days) and the second stopped gradually (over 15–30 days). Both groups were followed for 3.5 years. The relapse rates are shown in Table 21.1.

Over the first year, those who stopped lithium abruptly were three times as likely to relapse compared with those who stopped gradually, but the rate of relapse was the same in both groups after one year. Overall, those who stopped lithium gradually were substantially more likely to remain in remission than if they had stopped lithium abruptly. The average time to relapse was six months for the 'abrupt stoppers', and 15 months for the 'gradual stoppers'.

The second study (Baldessarini et al, 1997) followed 78 people with bipolar disorder over two years. Again, one group stopped lithium abruptly (over

Table 21.1
Relapse rates after lithium withdrawal

	Gradual withdrawal (15–30 days)	*Abrupt withdrawal (one to–14 days)*
Bipolar I	78% had relapsed at 3 years	100% had relapsed within 3 years
Bipolar II	50% had relapsed at 3.5 years	100% had relapsed within 3.5 years

one to 14 days) and another group stopped gradually (over 15–30 days). The 'time to relapse' was nearly six times as long for the gradual stoppers (14 months) compared with abrupt stoppers (2.5 months). Around 95% of the abrupt stoppers relapsed within two years, whereas only 69% of the gradual stoppers had relapsed by this time.

In the first study, 50% of those who relapsed after abrupt withdrawal did so within two to 10 weeks. Since lithium is completely eliminated from the body in approximately seven days, the high relapse rate over the time frame described cannot be exclusively a 'drug withdrawal' effect.

In the light of the evidence presented here, it would seem prudent always to withdraw lithium treatment gradually, over at least four weeks (if not longer).

Patients may decide that they wish to stop taking lithium for a variety of perfectly valid reasons (eg being well for a long time, lack of effect, side-effects). Abrupt discontinuation clearly adds a substantial and clinically important additional risk of early relapse. NH should be advised to recommence lithium immediately, and then either continue with treatment or discontinue gradually after a full discussion of the potential risks and benefits to her and her planned baby.

3. What problems might be anticipated when lithium is taken during pregnancy?
Lithium is known to cross the placenta readily and cases of neonatal cardiac arrhythmia, hypotonia and hypothyroidism have been reported [see review by Schou (1990)]. A raised incidence of fetal malformations caused by exposure in the first trimester has also been reported and lithium is widely considered to be a teratogen. This is largely because the Danish register of lithium babies, which was operated on a system of

retrospective voluntary reporting, found that 25 of the first 225 births recorded were associated with major congenital malformations. Ebstein's anomaly (a rare congenital downward displacement of the tricuspid valve into the right ventricle) was found in six of these babies and other cardiac abnormalities in a further 12 (Frankenberg and Lipinski, 1983). However, retrospective voluntary reporting attracts a disproportionate number of adverse outcomes and it is impossible to quantify the risks of lithium without knowing the total number of babies exposed and the number of adverse outcomes that were not reported. A more recent 148-patient prospective study (Jacobson et al, 1992) found that congenital malformation rates with lithium (2.8%) were similar to control rates (2.4%) and suggested that lithium is not an important human teratogen. It should be noted, however, that one case of Ebstein's anomaly was diagnosed at 16 weeks' gestation in the fetus of a patient taking lithium and the pregnancy was terminated. Also, echocardiographs were performed in less than half of the babies born, and so it is possible that minor cardiac defects went undetected.

This study would suggest that lithium is not as teratogenic as is widely believed. The authors suggest that, provided level II ultrasound and fetal echocardiography are performed, women exposed to lithium during pregnancy should not be at undue risk of an adverse outcome. It is also of interest that 21 of the lithium-exposed babies in this study were followed up after birth. They did not differ from a control group in their achievement of major developmental milestones. Nevertheless, the situation is far from clear and the teratogenic potential of lithium remains uncertain. Some caution is obviously required.

Prospective mothers should be afforded the opportunity to make an informed assessment as to the relative risks and benefits of continuing or discontinuing maintenance lithium. Since the fetal heart is formed early in pregnancy, stopping lithium once pregnancy is confirmed may be too late to prevent any lithium-induced heart defects.

A recent retrospective study has investigated the possible outcomes of either continuing or discontinuing lithium (Viguera et al, 2000). The recurrence rates for 101 women with bipolar disorder were noted during

pregnancy and postpartum (n = 42), or during equivalent periods (weeks one to 40 and 41-64) for control non-pregnant women (n = 59), for discontinuation of lithium. It was noted that:

- The relapse rates at 40 weeks after lithium discontinuation were similar for pregnant (52%) and non-pregnant (58%) women, but much higher than the year before discontinuation (21%), so pregnancy is relatively 'risk neutral' but rates of relapse increased sharply postpartum.
- Women who remained stable over the first 40 weeks after lithium discontinuation were 2.9 times more likely to relapse than non-pregnant women during weeks 41-62 (70% versus 24%).
- The relapse rates were higher in rapid (one to 14 days) rather than gradual (15-30 days) lithium discontinuation.
- The 50% relapse rate within 35 weeks is high and, therefore, the risk from consequentially needed drugs is high.
- There were no major malformations in the children born to the women (n = 9) who continued lithium throughout pregnancy.

Another important consideration is that renal clearance is increased during pregnancy and higher doses of lithium may be required to maintain therapeutic serum levels. Thus, regular close monitoring is essential. Particular care should be taken around the time of delivery, as changes in fluid balance can lead to sudden changes in plasma levels, placing both the mother and the neonate at risk. Some prescribers choose to stop lithium before delivery and restart within 48 hours in order to minimize both the risks above and the risk of relapse in the mother. It is not always possible to plan with such precision.

Some sensible guidelines on the use of lithium in pregnancy are included in an article by Cohen et al (1994).

Key points

- Long-term lithium prophylaxis markedly reduces the excess mortality of people with recurrent affective disorders.
- Although subject to debate, it is unlikely that those who discontinue treatment with lithium will subsequently fail to respond.
- The risk of recurrence of mania may be up to 28 times higher in the first three months after lithium

is stopped than it is for those who continue with treatment. This recurrence rate may exceed that of untreated bipolar illness.

- Relapse rates are greater after abrupt withdrawal (one to 14 days) than gradual withdrawal (15–30 days).
- Lithium readily crosses the placenta and dose-related side-effects may occur in the neonate.
- Lithium may not be as teratogenic as is commonly believed.
- The risk of fetal cardiac malformations cannot be excluded and all women exposed to lithium in pregnancy should undergo level II ultrasound and fetal echocardiography.
- The risk of relapse following discontinuation (and the risk from any drugs that may then be used to treat an acute relapse) may be higher than closely controlled continuation lithium during pregnancy.

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21

Rapid-cycling bipolar affective disorder

David Taylor

SC, a 33-year-old woman with a long history of bipolar affective disorder, including 11 previous hospital admissions, has currently been an inpatient for three months.

SC has not been observed to be euthymic throughout this period. Her mood changes rapidly from hypomania (characterized by sexual disinhibition and grandiosity) to depression and back again. Each period lasts only a few days. When depressed, SC ruminates about suicide and needs almost constant nursing observation. She has made two suicide attempts since being admitted, on one occasion drinking bleach and on another running head-first into a solid wall.

Her current medication is as follows:

Lithium carbonate (as Priadel)	*1200 mg at night*
Lofepramine	*210 mg at night*
Carbamazepine	*200 mg twice daily*

Questions

1. How might treatment be optimized?
2. What other drug alternatives are available?
3. Which 'experimental' therapies might be used in severe, refractory rapid cycling?

Answers

1. How might treatment be optimized?

SC is suffering from rapid-cycling bipolar affective disorder. This is usually defined by the occurrence of four or more episodes of hypomania or depression during a 12-month period (Dunner and Fieve, 1974). Up to 20% of bipolar patients presenting for treatment may have rapid-cycling illness (Coryell et al, 1992). It is more common in females. Rapid cycling is notoriously difficult to treat effectively.

Both pharmacological and non-pharmacological factors are associated with rapid cycling. Of these, the use of antidepressants, especially tricyclic antidepressants, is perhaps the most important: these drugs have frequently been implicated as precipitants of rapid cycling (Persad et al, 1996). However, it should be noted that an association has been disputed by Coryell et al (1992), who followed up prospectively a cohort of 919 patients with major affective disorders over a five-year period. Forty-five patients developed a rapid-cycling illness during the first year of this study and the authors concluded that the use of tricyclics or monoamine oxidase inhibitors (MAOIs) did not predict rapid cycling (after statistical control for the presence of major depression had been employed). They postulated that it is the episode of major depression that is predictive of the switch into rapid cycling, rather than the treatment that is administered (a so-called epiphenomenon).

Nevertheless, a logical first step in optimizing therapy for SC would be the withdrawal of lofepramine. Subsequent depressive episodes should be treated by psychological means, whenever possible.

Lithium, it has been suggested (Dunner and Fieve, 1974), is often ineffective in rapid cycling when used alone. However, there is some evidence to suggest that lithium given with carbamazepine shows synergy, at least in the treatment of mania (Lipinski and Pope, 1982; Kramlinger and Post, 1989). Lithium should therefore be continued and the dose adjusted, if necessary, to give a 12-hour plasma level of 0.6–1.2 mmol/l.

Carbamazepine is commonly used in bipolar disorder and has been shown to be effective in rapid cycling when added to lithium therapy and when used alone (Joyce, 1988). However, higher doses than 400 mg daily are usually required to produce a therapeutic effect. Indeed, it has been suggested that in bipolar disorder in general, doses of at least 600 mg daily should be used to give plasma levels >7 mg/l (Taylor and Duncan, 1997). Thus, a dose increase would be appropriate for SC. Modified-release tablets are better tolerated and should be used. The minimum dose should be that which gives a trough plasma level of 7 mg/l; the maximum dose is best governed by patient tolerability and response rather than plasma level.

2. What other drug alternatives are available?

In the UK, only lithium and carbamazepine are licensed as mood stabilizers. In the United States, valproate (as divalproex sodium) is also available and widely used. In the UK, divalproex is known as valproate semisodium. It is licensed in the treatment of mania. There is some compelling evidence that valproate is effective in rapid cycling when used alone or when added to lithium or carbamazepine, even if these therapies have proved ineffective (eg McElroy et al, 1988; Calabrese and Delucchi, 1990; Calabrese et al, 1992; Schneider and Wilcox, 1998). Valproate is therefore often recommended as first- or second-line therapy in rapid cycling, either alone or in combination (Calabrese and Woyshville, 1995; Taylor and Duncan, 1996). Average effective doses are around 1500 mg daily (Taylor and Duncan, 1997). Modified-release tablets seem to be better tolerated than other preparations. Valproate semisodium may also offer improved tolerability.

Other drugs available include clozapine, which is effective in treatment-refractory mania (Calabrese et al, 1996b) and appears to have some activity in rapid cycling (Suppes et al, 1994). Clozapine is licensed in the UK

only for treatment-refractory schizophrenia, although the manufacturers are sympathetic to requests for 'out of licence' use and consider each case individually.

Thyroxine also seems effective in rapid cycling (Stancer and Persand, 1982; Taylor and Duncan, 1996; Extein, 2000), although it should be noted that this is as an add-on to existing therapy. In some cases, efficacy has been shown when thyroxine has been used as an adjunct to antidepressants, fuelling the debate mentioned above (Bauer and Whybrow, 1990). Clonazepam may be effective in the maintenance treatment of bipolar disorder (Sachs et al, 1990). However, none of these treatments has been comprehensively evaluated and definitively shown to be effective. Further studies are needed and caution is advised when these medications are used.

3. Which 'experimental' therapies might be used in severe, refractory rapid cycling?

Rapid cycling is so often unresponsive to standard treatments that many other putative, experimental therapies have been investigated. They include nimodipine, lamotrigine and gabapentin. None is officially licensed for use in bipolar disorder and none has been robustly evaluated in rapid cycling. Nevertheless, these experimental drugs are frequently used as a last resort in refractory cases. Despite the inherent unresponsiveness of these patients, a worthwhile response is sometimes observed.

Nimodipine is a centrally acting calcium antagonist usually used in the treatment of subarachnoid haemorrhage. A small double-blind trial first suggested activity (Pazzaglia et al, 1993) and this finding has subsequently been supported by case reports (Goodnick, 1995). Doses of 30–60 mg tds are initially used and may be effective. Up to 360 mg daily has been used. Adverse effects are infrequent and trivial.

Lamotrigine is a relatively new anticonvulsant which has for some time been considered potentially useful in mood disorders. Calabrese et al (1996a) were the first to report a case of response to the drug in rapid cycling. Antidepressant effects were particularly evident. Other case series have since been reported. Kusumakar and Yatham (1997) reported successful treatment in four of seven rapid-cycling patients and Sporn and Sachs (1997) described good outcome in eight of 16 patients with refractory bipolar

disorder (four of the eight were rapid cyclers). More recently, a large randomized controlled trial clearly demonstrated that lamotrigine has important efficacy in rapid cycling (Calabreze et al, 2000) and it is increasingly being seen as an early-use option for this condition. Slow introduction of lamotrigine is essential to avoid rash. Doses in responders average around 150 mg daily.

Gabapentin, another recently introduced anticonvulsant, may also be effective. At least two case series have been published (Bennett et al, 1997; Schaffer and Schaffer, 1997), broadly indicating good activity in refractory mood disorders. Neither report provided much information relating specifically to rapid cycling. A later open trial (n = 37) also suggested that gabapentin might be effective (Young et al, 1999) and choline has also been suggested as being effective (Stoll et al, 1996).

Case reports and open studies of experimental treatments should be interpreted with due consideration of the prognosis of rapid-cycling illness. The study by Coryell et al (1992) found that while patients with rapid-cycling illness had a significantly lower likelihood of recovery in the second year of follow-up, the prognosis improved significantly after this time, with only one of 45 patients exhibiting a rapid-cycling illness for the entire five-year follow-up period. The remission rate was high in years three to five, and so case reports featuring patients apparently 'responding' at this stage in their illness should be treated with particular caution.

Key points

- Up to 20% of bipolar patients presenting for treatment have had four or more episodes of hypomania or depression during the previous 12 months (rapid cycling).
- Antidepressants may precipitate rapid cycling.
- Lithium is often ineffective when used alone but may offer benefit in combination with carbamazepine.
- Valproate preparations may be effective, either alone or in combination with lithium or carbamazepine.
- Unlicensed options worth considering in patients with refractory illness include thyroxine, clozapine, nimodipine, lamotrigine and gabapentin.

- **Patients with rapid-cycling illness have a poor prognosis in the short term, but it is likely that only a very small proportion continue to cycle rapidly for more than a few years.**

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22

Antidepressant-induced switching in bipolar affective disorder

Shameem Mir

CM, a 27-year-old Caucasian woman, was brought to the emergency clinic of her local psychiatric hospital by the police on a Section 136. The police had been called to a restaurant where CM had refused to pay for an expensive meal. She had been running around the restaurant bare-footed, brandishing a scarf above her head. When she arrived at the hospital CM was euphoric and exhibited pressure of speech and flight of ideas. She was scantily clad in flamboyant clothes, was wearing heavy, bright make-up and her hair was somewhat dishevelled.

CM's first psychiatric admission was nine years ago with a diagnosis of mania which responded to antipsychotic treatment. Her second episode of mania was a year later and also resulted in hospital admission. This time lithium alone was prescribed to which CM responded well. CM had been stable on lithium for the first two years but then started to suffer from major depressive

episodes. Over the last six years she has had five admissions; three for major depression and two for hypomania, both of which occurred around six to eight weeks after starting antidepressant treatment (amitriptyline and then fluoxetine). During CM's last admission (12 weeks ago) she was prescribed venlafaxine 75 mg daily, the dose of which had been cautiously increased over two months to 75 mg twice a day. CM had been prescribed this dose for four weeks prior to her current presentation.

CM had no significant medical history. Her mother had a diagnosis of bipolar affective disorder.

CM's drug regime on admission was:

Lithium carbonate	600 mg at night
Venlafaxine XL	150 mg twice a day

A physical examination and routine blood tests were unremarkable. CM's lithium level on admission was 0.6 mmol/l (and has been fairly stable around this level since she started lithium treatment). A urine drug screen proved negative.

CM's diagnosis was hypomania, probably induced by antidepressants.

Questions

1. What is antidepressant-induced switching?
2. What are the risk factors?
3. What are the treatment options for CM?

Answers

1. What is antidepressant-induced switching?

Switching is the induction by antidepressants of mania or hypomania in patients with unipolar or bipolar disorder. It can also indicate an antidepressant-induced increase in cycle rate.

The major problem in trying to establish the frequency of antidepressant-induced mania is the possibility that any 'switch' could be part of the natural course of the illness. It is generally accepted that all antidepressants have the potential to induce mania or accelerated cycling, but there are few data comparing the incidence or severity of these effects between the different classes of antidepressants. One of the reasons for such scant data is that clinical trials involving antidepressant drugs often exclude patients with a history of bipolar disorder. In addition, large clinical trials of antidepressants in combination with mood stabilizers have not been conducted since the early 1980s.

The studies conducted to date have many shortfalls: early studies did not separate bipolar and unipolar patients; few were placebo controlled; phases of illness differed between acute and continuation therapy; those taking mood stabilizers were not separated from those who were not; some groups contained a higher proportion of women; and those studies conducted in tertiary referral centres may have included 'difficult to treat' patients who may be more prone to switching. With these caveats in mind, the following studies are of note.

A switch rate of 41% has been reported in untreated bipolar patients (Lewis and Winokur, 1982), which perhaps provides a 'baseline' rate for switching. In unipolar patients, however, one might expect the switch rate to be lower. In a review of 15 placebo-controlled studies that included over 1200 patients (Rouillon et al, 1992) the switch rate in unipolar patients randomized to receive tricyclics was 1–5%, compared with 0–9% of those randomized to receive placebo. Of the 158 patients diagnosed as having bipolar illness, the switch rate was reported as 23% with placebo, 21% with lithium alone, 28% with lithium in combination with a tricyclic and 51% with a tricyclic alone. These results would indicate that half of the switch rate in this patient group may be due to the natural course of the illness, and the other half due to treatment with tricyclics, or perhaps simply the occurrence of depression severe enough to warrant the prescribing of an antidepressant.

In a retrospective study of patients with refractory bipolar illness, Altshuler et al (1995) concluded that mania was likely to have been induced by antidepressants in one-third of cases and cycle acceleration in a quarter. These

observations were supported by a later naturalistic, prospective study [cited by Post et al (1997)].

Peet (1994) compared the incidence of switch into mania using pooled data from trials of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and placebo. For those with unipolar illness the switch rates for SSRIs, TCAs and placebo were 0.72, 0.52 and 0.21%, respectively. For those with a bipolar illness, the switch rates were 3.7, 11.2 and 4.2%. From this, Peet concluded that SSRIs were the antidepressants of choice in those with a history of bipolar disorder.

Peet's finding with regard to a higher switch-rate in bipolar patients with TCAs compared with SSRIs have since been supported by Bottlender et al (2000). His observed switch-rates in unipolar patients, however, are contradicted by Barak et al (2000). This latter group found that the rate of SSRI-induced mania was indeed lower than TCA-induced mania in unipolar depression (0.15% versus 1.29%).

Vesely et al (1997), however, advised caution in the use of SSRIs. They reported six cases of SSRI-induced mania (four of which were associated with above maximum recommended BNF dose of antidepressant). In addition, an earlier report describes 11 cases of drug-induced mania with fluoxetine, paroxetine or sertraline (Howland, 1996). Clearly, switching may follow the use of SSRIs but the incidence of this is probably significantly lower than with TCAs.

Case reports of antidepressant withdrawal precipitating hypomania have also been published (eg Nelson et al, 1983; Gupta and Narang, 1986). Such reports are infrequent and difficult to interpret. The withdrawal of lithium may also precipitate a manic episode (Schou, 1993). Mania after carbamazepine withdrawal has also been reported (Scull and Trimble, 1995).

2. What are the risk factors?

Antidepressant-induced cycle acceleration

Altshuler et al (1995) found that antidepressant-induced cycle acceleration was associated with younger age when first treated and more likely to occur in women [this was later supported by Simpson and Liebowitz, (1996)]. They also found bipolar patients to be particularly at

risk. Altshuler et al (1995) also described the course of illness in a treatment-refractory cohort of patients. Such patients are likely to have an illness pattern in which mania follows depression (Faedda et al, 1991) and this should be considered when interpreting their results.

Antidepressant-induced switching to mania or hypomania

In a recent study, Henry et al (2001) looked specifically at risk factors for antidepressant-induced mania in bipolar patients. They found that sex, age and diagnosis (bipolar I versus bipolar II) did not affect the risk of switching. In addition, the frequency or severity of symptoms such as psychotic, melancholic and catatonic did not differ significantly between patients who did and did not switch. Interestingly, from their observations of 43 patients with antidepressant-induced mania or psychosis, Preda et al (2001) suggest a past history of psychosis to be a major risk factor. Henry et al (2001) concluded that a personal or family history of hypomania or mania and a high score on the hyperthymic temperament scale are major risk factors for antidepressant-induced switching in bipolar patients.

In addition to these findings, Henry et al (2000) also suggested that lithium was perhaps the most effective mood stabilizer in preventing antidepressant-induced mania. This has been supported to some extent by another recent study by Bowden et al (2000), who found no difference in switch rates between patients on valproate and those not on valproate, but did find a difference in switch rate between these two groups and those on lithium; however, although the difference was large it was not statistically significant.

3. What are the treatment options for CM?

CM has a diagnosis of bipolar affective disorder. She has had five hypomanic episodes (three thought to be anti-depressant-induced) and three episodes of depression over the previous nine years. CM has been taking lithium carbonate for the past eight years and although it kept her well for the first two years, it did not prevent antidepressant-induced hypomania.

There are three aspects of CM's treatment that need to be considered:

1. Treatment of hypomania
2. Treatment of bipolar depression
3. Prophylaxis.

Ideally, a mood stabilizer should be effective in treating all of the above.

Treatment of mania

The first step would be to abruptly stop the antidepressant venlafaxine. In cases of suspected antidepressant-induced mania, gradual withdrawal of antidepressants is not recommended, despite the possibility of discontinuation symptoms.

Lithium has been used as a mood stabilizer in bipolar affective disorder for almost 50 years. It is still considered as first-line treatment in acute mania and for prophylaxis by some, but others doubt its effectiveness in clinical practice. Moncrieff (1997) questioned the efficacy of lithium in the treatment of acute mania, unipolar and bipolar disorders. Cookson (1997) argued that lithium is effective in some patients for prophylactic therapy in bipolar disorder and that it is important to establish whether the patient is a 'lithium responder' first. During her second hypomanic episode CM responded to lithium alone, which suggests that she is a 'lithium responder'.

Since then CM's lithium levels have never exceeded 0.6 mmol/l. Her symptoms of hypomania may resolve with higher lithium levels. This may then preclude the need for polypharmacy or changing her mood stabilizer. The next step, therefore, would be to optimize CM's lithium treatment.

Indeed, expert consensus for the medication treatment of bipolar disorder (APA, 2000) advise using lithium as first-line treatment for mania presenting without dysphoria or psychosis. Lithium may take seven to 10 days to exert its antimanic effect and so the addition of a benzodiazepine may be prudent in the acute phase.

Should CM show no response to higher doses of lithium, an alternative mood stabilizer such as valproate or carbamazepine, or the addition of one of these drugs to her current regimen, may be considered.

Valproate's effectiveness compared with placebo in acute mania has been shown in a large, controlled trial (Bowden et al, 1994). Carbamazepine is also thought to be effective in treating mania (Young and Calabrese, 2000).

The use of antipsychotics is justifiable only where psychotic symptoms are

present. Antipsychotics may exacerbate post-manic depression and there is little evidence to support their long-term use (discussed further under prophylaxis).

In summary, the best course of action is to stop venlafaxine, increase the dose of lithium and consider short-term use of a benzodiazepine. If there is no response then change the (or add another) mood stabilizer.

Treatment of bipolar depression

For a mild to moderate depression, or for a patient whose initial manic episode was precipitated by an antidepressant, experts (APA, 2000) show preference for the use of a mood stabilizer alone. Mood stabilizer monotherapy is also preferred for first episode bipolar depression in unmedicated bipolar patients. Combining a mood stabilizer with an antidepressant follows a close second.

The American Psychiatric Association (APA, 2000) recommend using lithium either alone or in conjunction with an antidepressant, as do Compton and Nemeroff (2000), who state that lithium is the most appropriate initial treatment for the depressive phase of bipolar disorder and that other mood stabilizers have shown only preliminary efficacy. In contrast, Nolen and Bloemkolk (2000) opine that there is no proof for the efficacy of lithium, carbamazepine and sodium valproate in bipolar depression, but that evidence does exist for lamotrigine. Indeed, lamotrigine's efficacy for bipolar depression has been shown in nine randomized controlled trials (Calabrese et al, 1999).

Muller and Grunze (2000) strongly argue against using a mood stabilizer alone for the treatment of bipolar depression. They feel that the restrictions imposed on the use of antidepressants in treatment guidelines are excessive. They express concern over the strength of the evidence that mood stabilizers treat depression and feel that the risk of suicide secondary to untreated depression outweighs the fear of antidepressant-induced mania.

With little or no response to a mood stabilizer, the addition of an antidepressant should be considered. There is general consensus in the choice of antidepressant. Bupropion (amfebutamone) and the selective serotonin reuptake inhibitors (SSRIs) are thought to be less likely to

precipitate a switch to mania compared with the tricyclics (APA, 2000; Compton and Nemeroff, 2000; Nolen and Bloemkolk, 2000). In addition, the expert consensus (APA, 2000) avers that venlafaxine also has a lower propensity to induce switching [although reports of mania have been published, e.g. Wilson and Jenkins, (1997)].

Electroconvulsive therapy (ECT) has been found to be highly effective in bipolar depression (Compton and Nemeroff, 2000), and for refractory patients Nolen and Bloemkolk (2000) recommend using the monoamine oxidase inhibitor (MAOI) tranylcypromine.

In summary, the best course of action might be to optimize the mood stabilizer and, if necessary, cautiously add an SSRI or perhaps bupropion (amfebutamone). Bupropion is not licensed as an antidepressant in the UK.

Prophylaxis

All the well-established mood stabilizers (lithium, carbamazepine, valproate) seem to be more effective in treating and preventing acute mania than depression. Indeed, evidence for their efficacy in prophylaxis is not cogent.

Lithium has been shown to have specific antisuicidal properties (Goodwin, 1999). An important consideration given that the suicide rate amongst those with bipolar affective disorder is 15% (Compton and Nemeroff, 2000). There are randomized controlled trials investigating the efficacy of carbamazepine for prophylaxis, but the evidence is not strong. With valproate (usually in the form of valproate semisodium) the evidence is based on open data and one randomized controlled trial in patients with heterogenous affective disorders (Young and Calabrese, 2000). In another recent trial, Bowden et al (2000) failed to show that valproate prolonged the time to relapse (hypomania/mania or depression) over a 12-month period.

The American expert consensus (APA, 2000) for maintenance treatment after a manic episode is to continue to treat with the same mood stabilizer that had been effective in treating the acute phase.

If antipsychotics were necessary to treat psychotic symptoms during the acute phase, it is common (and good) practice to withdraw them once manic symptoms resolve. Some patients may benefit from long-term treatment with

antipsychotics. In this situation atypical antipsychotics are preferable (with typical antipsychotics the risk of tardive dyskinesia should be borne in mind). Olanzapine and risperidone have both been shown to be effective in acute mania (Young and Calabrese, 2000).

In summary, continue with the mood stabilizer that effectively treated mania/hypomania.

Key points

- Switching is the induction by antidepressants of mania or hypomania in patients with unipolar or bipolar disorder.
- Risk factors include a history of bipolar illness and a high score on the hyperthymic temperament scale.
- Lithium has a protective effect.
- Bupropion and SSRIs may be associated with a lower risk than the tricyclics.
- Bipolar patients should ideally be maintained with mood-stabilizing drugs alone.
- Antidepressants should generally be reserved for severe depressive episodes.

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23

Atypical antipsychotics in bipolar disorder

Petrina Douglas-Hall

WH, a 25-year-old Caucasian man with a four-year history of bipolar affective disorder, is noted by his community psychiatric nurse to be more irritable than usual and an appointment was made for him to see a psychiatrist. He is found to be sleeping less, has poor concentration and was making sexual advances to females in the street. A mental state examination showed he had a flight of ideas and pressure of speech. A urine screen ruled out the use of illicit drugs and a diagnosis of manic phase of bipolar disorder was made. His medication was lithium 800 mg at night, which produced a 12-hour post-dose plasma level of 0.9 mmol/l. WH had remained well on lithium for the past year and was known to be fully compliant with medication.

WH had suffered one depressive and four manic episodes in the past four years. He had been previously treated with haloperidol and chlorpromazine, and was known to have a low threshold for developing extrapyramidal side-effects

(EPSEs). He had also been treated with the mood stabilizers lithium and sodium valproate. It was documented in his notes that he had responded poorly to carbamazepine.

The assessing psychiatrist decided to add olanzapine 10 mg at night to his existing lithium. The olanzapine was titrated up to 20 mg within a week. After two weeks of treatment, a significant improvement in WH's mental state was noted and at four weeks he was said to be in remission.

WH remained well for four months on a combination of lithium 800 mg and olanzapine 20 mg at night. At this point his mental state began to deteriorate again. His lithium level was 0.95 mmol/l and he was thought to be compliant with olanzapine. Sodium valproate was added to WH's existing medication. The dose was titrated until a plasma level of 70 mg/l was achieved but, after six weeks at this level, WH remained unwell. The clinical team are now considering initiating treatment with clozapine.

Questions

1. Why use atypical antipsychotics in bipolar affective disorder?
2. What is the evidence supporting the use of atypical antipsychotics in bipolar affective disorder?
3. Is clozapine the logical next step for WH?

Answers

1. Why use atypical antipsychotics in bipolar affective disorder?

The mood stabilizers lithium, valproate and carbamazepine are generally considered to be first-line treatments in both mania and the prophylaxis of bipolar disorder (APA, 1994; Sachs et al, 2000). The evidence base underpinning these treatments is poor and up to a third of patients develop chronic symptoms (Young and Calabrese, 2000). Other treatment options are clearly required. Psychotic symptoms are common in mania and

antipsychotic drugs are frequently prescribed in clinical practice.

It has been reported that bipolar patients are at increased risk of developing tardive dyskinesia (TD) with conventional antipsychotics (Mukherjee et al, 1986) and that male patients with mania have a greater risk of developing acute dystonia than patients with schizophrenia (Nasrallah et al, 1988). Compared with the typical antipsychotics, the atypicals have a lower tendency for causing EPSEs (Stanniland and Taylor, 2000) and arguably TD, although for the latter most evidence relates to olanzapine (Tollefson et al, 1997). Clozapine, however, may even reverse the effects of TD (Lieberman et al, 1991). Interestingly, Calabrese et al (1996), in study of a clozapine in treatment-resistant mania, reported that of the six patients who had TD at the beginning of the trial, all showed improvements in their symptoms within 30–45 days.

Atypical antipsychotics may, therefore, be better tolerated than the older drugs in patients with bipolar illness: well-designed, long-term trials are needed to confirm this. WH was known to be sensitive to EPSEs, making an atypical antipsychotic an appropriate choice for him, although it may have been more appropriate to have added a second mood stabilizer and used a benzodiazepine for sedation at this stage.

2. What is the evidence supporting the use of atypical antipsychotics in bipolar affective disorder?

Olanzapine is licensed for the treatment of acute mania associated with bipolar I disorder in the USA, but not as yet in the UK. Olanzapine was granted this licence based on two double-blind, placebo-controlled trials by Tohen et al (1999, 2000).

The first trial involved 139 patients randomized to receive either olanzapine or placebo for three weeks (Tohen et al, 1999). Forty-nine per cent of the olanzapine group responded to treatment compared with 24% of the placebo-treated group. Olanzapine was started at 10 mg daily and its effect was evident at week three. The second trial involved 115 patients again randomized either to olanzapine or placebo (Tohen et al, 2000). Sixty-five per cent of the olanzapine group responded to treatment compared with 43% of the placebo-treated group. In this trial olanzapine was begun at 15 mg daily and its effect was evident after week

one, and was maintained for four weeks (the duration of the trial). In both trials, the maximum dose of olanzapine used was 20 mg and response to treatment was defined as 50% or more improvement in the Young Mania Rating Scale (YMRS) (Young et al, 1978). Interestingly, patients with and without psychotic symptoms responded similarly to olanzapine's antimanic effect, as did patients presenting with a manic or mixed episode.

Currently, there are no published controlled trials that include an active comparator drug. While it is interesting to note that olanzapine is more effective than placebo, more robust trials that include another active treatment arm are required. At the time of writing, there are no studies that examine the efficacy of olanzapine as an adjunct to mood stabilizers or as prophylaxis against further episodes of mania.

There are several case studies and open uncontrolled trials suggesting that risperidone may be effective when used as monotherapy or as adjunctive therapy to mood stabilizers for manic episodes. Currently, there is only one published double-blind controlled study (Segal et al, 1998). This study found that risperidone at a dose of 6 mg daily was just as efficacious as haloperidol at a dose of 10 mg daily or lithium in the treatment of acute mania over 28 days. However, the sample size was small, involving just 45 patients in total, which may not have enabled significant differences to be elucidated. Also, mean plasma lithium levels were 0.53 mmol/l at day seven, 0.62 mmol/l at day 21 and 0.72 mmol/l at day 28. These levels may be considered to be rather low for the treatment of an acute episode of mania.

There are no double-blind, randomized, placebo-controlled trials of risperidone. Keck et al (2000b) investigated the placebo response rate in studies looking at the treatment of acute mania and bipolar depression. They concluded that trials that omitted a placebo control group were of little use because of the high placebo response rate.

There are no double-blind controlled trials for quetiapine in bipolar affective disorder. There are case series and case reports that support the efficacy of quetiapine in the treatment of mania, mixed affective states and psychotic depression. These reports are difficult to interpret, as the majority of patients also received mood stabilizers,

antidepressants or other psychotropic drugs (Ghaemi and Katzow, 1999; Zarate et al, 2000).

There is one unpublished double-blind placebo-controlled trial investigating the use of ziprasidone in the treatment of acute mania over three weeks (Keck et al, 2000a). Ziprasidone (80–160 mg daily) was shown to significantly improve manic symptoms on day two of treatment. This improvement was maintained to the endpoint of the trial.

One study by Harada and Otsuki (1986) suggested that zotepine and lithium used together were effective in the treatment of mania only for patients who subsequently become depressed. The incidence of EPSEs and other side-effects was high. Much of the published work regarding zotepine is in languages other than English and few translations are available.

3. Is clozapine the logical next step for WH?

Arguably, yes. Electroconvulsive therapy (ECT) may also be considered (Sachs et al, 2000).

There is no general consensus on the definition of treatment-resistant mania or bipolar disorder. For different trials the definition of treatment resistance varies, making the comparison of studies difficult. For example, Calabrese et al (1996) took treatment resistant to mean intolerance or non-response to a six-week trial of lithium (plasma level $\geq$0.8 mmol/l), plus a poor response to either valproate ($\geq$50 mg/l) or carbamazepine ($\geq$6 mg/l) and two antipsychotics. In the trial conducted by Suppes et al (1999), subjects did not respond to two simultaneous mood stabilizers at therapeutic levels and, if psychosis was present, failure of treatment with a typical antipsychotic in combination with a mood stabilizer was required. Intolerance of medication also justified subjects being classed as treatment resistant in this latter trial.

WH has not responded to mood stabilizers either as monotherapy or as combination therapy. He is intolerant of haloperidol and chlorpromazine and is currently not responding to olanzapine. Although benzodiazepines may help in the short term they are not a long-term solution. WH may be considered as being treatment resistant. It could be argued that clozapine is justified (Sachs et al, 2000). Although clozapine is not licensed for this indication, the Clozaril Patient Monitoring Service will consider

individual cases on merit and facilitate 'out-of-licence' use in clinically appropriate patients.

There have been no double-blind controlled trials of clozapine in bipolar disorder. There are, however, numerous open studies and case series. These studies suggest that clozapine is effective in the treatment of acute mania and maintenance therapy, particularly in treatment-resistant populations. In these populations, placebo response is rare, so case reports have some validity.

Barbini et al (1997), in an open prospective randomized trial for acute mania, suggested that clozapine may have a faster onset of action than chlorpromazine. However, superior efficacy at week two was not maintained at week three. Both drugs were used alongside lithium. Calabrese et al (1996), in an open uncontrolled study, indicated there may be a role for clozapine monotherapy in treatment-resistant mania (which also included rapid cycling). Green et al (2000) suggested that clozapine was effective for treatment-resistant psychotic mania. For maintenance therapy, Suppes et al (1999) have demonstrated, in a year-long open prospective randomized trial, the advantages of adding clozapine to existing medication in treatment-resistant bipolar illness. Clozapine was shown to be an acute and prophylactic antimanic agent with limited antidepressant action.

In summary, olanzapine is currently the only atypical antipsychotic licensed for the treatment of acute mania, albeit in the USA. No atypical antipsychotics are licensed for maintenance treatment. For clozapine, risperidone and ziprasidone there is evidence suggesting efficacy in acute mania. Although robust double-blind trials are still needed for clozapine, it may be argued that clozapine is justified and should be used in the treatment of acute and long-term treatment-resistant mania. It may be an appropriate treatment option for WH.

The dosing of clozapine is similar to that for the treatment of schizophrenia. Once WH has been stabilized on clozapine, the sodium valproate may then be reduced gradually and stopped, as he showed no response to this drug.

Key points

- Most evidence pertains to olanzapine in the treatment of acute mania.

- **No atypical antipsychotics have demonstrated efficacy in the treatment of bipolar depression.**
- **Clozapine may be considered for treatment-resistant mania. It may also have mood stabilizing properties.**

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24

Depression in the elderly

Denise Taylor

VF, an 88-year-old woman with a diagnosis of severe depression, was admitted to hospital from home. VF has no formal documented history of depression but admits to a period when younger 'where everything was going wrong'. She thinks that her mother had problems with depression in later life. Her daughter has received treatment for depression as an adult. VF's GP requested an urgent referral to the Community Mental Health Team (CMHT) for assessment 10 days prior to admission, at the same time prescribing a small dose of amitriptyline (25 mg at night which VF has since stopped taking as it was not 'doing any good').

VF was extremely anxious about being 'admitted to an institution for mental people' and thought she may never be discharged. On questioning she admitted to having had sleep disturbances (early morning wakening) for a few months, being unable to concentrate and feeling anxious. She had lost one stone in weight over the last month,

admitted to not wanting to continue with life and had thought about taking an overdose.

On observation VF had obvious signs of weight loss; looked unkempt with dishevelled hair and in general appearance, and was very restless.

VF had had a hip replacement five years previously but otherwise was fit and well. She was a keen and accomplished pianist and until recently had still been teaching. Three months previously, VF's husband had been admitted to a nursing home for the treatment of end-stage Alzheimer's disease. Prior to this, VF was the sole carer of her husband at home. She eventually stopped visiting him in hospital as she felt that he was no longer the man she used to know. VF has two children and she feels close to her son but has a 'difficult' relationship with her daughter. She has been staying with her son and his partner because she does not want to be left on her own in her own home. She feels that 'terror and defeat are staring her in the face' and that she could do herself harm if left on her own.

On the Geriatric Depression Rating Scale (GDS), VF scored 24 out of 30 (severe depression). Physical examination and routine blood tests were unremarkable. Cognition was grossly intact.

Medication prescribed on admission was as follows:

Paroxetine 10 mg mane to increase to 20 mg in four days
Diazepam 2 mg mane
Zopiclone 7.5 mg nocte

Concomitant therapy was as follows:

Close observation
Breathing and relaxation techniques
Distraction therapy

One month post-admission VF was joining the group for meals and sitting in the television room occasionally. She went out with her son for the day but came back 'a bag of nerves', finding the crowds and open spaces very frightening.

Questions

1. Discuss the difficulties of diagnosing depression in the elderly.
2. Discuss first-line antidepressant therapy in the elderly with particular reference to efficacy, safety and tolerability.
3. What factors influence dosage choice, duration of therapy and withdrawal requirements of antidepressants in the elderly?
4. Discuss the various social issues that must be resolved before VF can be discharged home.
5. What is the role of adjuvant medication such as benzodiazepines and hypnotics in treating the elderly depressed?

Answers

1. Discuss the difficulties of diagnosing depression in the elderly.

Depression is common in the elderly, with a prevalence of 15% in the community, 25% in the general practice population and >30% in residential or long-stay care facilities (Macdonald, 1997). Recognition and diagnosis of depression is often poor in this age group because of the presence of masking ageing factors such as: reduced psychomotor function, sleep-pattern disturbance, constipation, loss of appetite and increasing social isolation (Royal Society of Medicine, 1999). Symptoms may also be masked by pain, anxiety, impaired cognitive function, agitation, behavioural disturbances and hypochondriasis. Untreated, depression is a major risk factor for increased morbidity and mortality in this age group, and the patient can rapidly slip into a state of self-neglect with starvation, dehydration and/or hypothermia, and resultant physical and social withdrawal leading to skeletal muscle contractures and venous stasis. Suicide is a major concern, with attempted suicides generally being serious bids rather than parasuicidal gestures typical of young adults. Elderly patients account for some 19% of all suicides (Cattell and Jolley, 1995).

Depression often exists with chronic illness and is particularly associated with Parkinson's disease, dementia,

certain endocrine disorders and cardiovascular disease. Co-morbidity may make diagnosis of depression more difficult but should not preclude active treatment (Katona and Livingston, 2000). Depression is not a part of normal ageing as some 85% of the general ageing population do not experience depression. Certain medications may also cause depression in their own right and therefore a medication review should be undertaken to preclude this possible cause (Lader, 2000).

An accurate diagnosis is dependent on a complete history taking, including: medication, physical illness, psychological history, rigorous mental state examination and social circumstance.

2. Discuss first-line antidepressant therapy in the elderly with particular reference to efficacy, safety and tolerability.

It is well documented that there is little difference in efficacy of any group of antidepressants when used at a therapeutic dosage (Geddes et al, 2001; Wilson et al, 2001). Therefore, treatment decisions about which pharmacological agent to use are dependent on patient acceptability, tolerability, toxicity, suicide risk and cost (Mittman et al, 1997; Barbui et al, 2001; Geddes et al, 2001).

The elderly are most susceptible to the adverse effects of any medication because of age-related changes in pharmacokinetic and pharmacodynamic parameters. These changes may then be exacerbated by concomitant medication and/or pathology. The pharmacokinetic profile of the selective serotonin reuptake inhibitors (SSRIs) varies between each agent, which may be clinically significant depending on patient factors. The long half-life of fluoxetine and its active metabolite norfluoxetine may delay time to steady state (and, therefore, in theory, full therapeutic effect) for one to three months (although there is no clinical evidence for this). Clearance of SSRIs in the elderly is generally unchanged, except for citalopram (reduced by at least 50%) and paroxetine (which undergoes extensive first-pass metabolism), which can result in higher plasma levels (Von Molke et al, 1993). The propensity of the SSRIs to cause serious medication interactions is dictated by their ability to inhibit hepatic cytochrome (CYP) isoenzymes. Sertraline and citalopram are less likely to inhibit these enzymes and therefore they may be the SSRIs of choice in the elderly (Edwards and Anderson, 1999).

The pharmacokinetic profile of tricyclic antidepressants (TCAs) is markedly altered in the elderly, with reduced clearance and prolonged elimination half-lives (Lancaster and Gonalez, 1989). These changes can lead to increased plasma concentrations and an increased risk of dose-related toxicity (Von Molke et al, 1993).

The adverse effect profile of each class needs to be taken into account before prescribing. With TCAs there are disease-related contraindications (recent myocardial infarction, arrhythmias or severe hepatic disease) and cautions (old age, urinary retention, glaucoma, epilepsy or renal impairment) that would preclude prescribing in certain elderly people. The adverse effects of TCAs are well known and include: anticholinergic problems (urinary retention, dry mouth, cognitive impairment, constipation, syncope, blurred vision) (Lancaster and Gonalez, 1989); postural hypotension (increased risk of falls and fractures, leading to increased morbidity and mortality), central side-effects (weakness, fatigue, tremor, delirium) (Von Molke et al, 1993) and cardiac toxicity (myocardial depression, type 1A antiarrhythmic activity).

There are no absolute disease-related contraindications to prescribing an SSRI. Cautions include: epilepsy, cardiac disease, diabetes, and a history of bleeding disorders, hepatic or renal disease. The adverse effects of SSRIs are generally gastrointestinal (nausea, vomiting, abdominal pain, anorexia, which may exacerbate weight loss in the elderly). hypersensitivity and others including hyponatremia, (especially in the elderly), headache, nervousness and anxiety. Each agent has a slightly different side-effect profile (Newhouse, 1996) and prescribers should familiarize themselves with these differences. For example, extrapyramidal side-effects (EPSEs) and tremor have been reported more frequently with paroxetine and fluoxetine (Edwards and Anderson, 1999), therefore it may be less wise to use these agents in patients with depression associated with a movement disorder such as Parkinson's disease. Fluoxetine, sertraline and paroxetine have low cardiovascular risks so these agents may be first-line options in patients who are post-myocardial infarction or those with arrhythmias such as atrial fibrillation (Glassman et al, 1998).

Medication interactions occur with both SSRIs and TCAs so it is important to select the most suitable individual agent

for a particular patient. Because of the narrow therapeutic range of TCAs, any interaction which causes a rise in plasma concentration has the possibility of causing death through cardiac instability. Therefore, these agents should be used with extreme caution in patients with concomitant interacting medicines and those with cardiac disease.

Elderly people with suicidal intent or ideation (Waern et al, 1999) should not be prescribed TCAs or even perhaps citalopram, which somewhat arguably has a higher associated lethality in overdose (Edwards and Anderson, 1999). It is extremely difficult to give blanket guidance on the choice of an antidepressant for all elderly people due to the heterogeneity of this population group. However, it would seem wise to use an SSRI as a first-line treatment (with the particular choice of agent dependent on patient factors, pharmacokinetic changes and tolerability), changing only to another pharmacological class once an adequate trial at a therapeutic dose has failed. There is some evidence that venlafaxine [a serotonin and noradrenaline reuptake inhibitor (SNRI)] may be more effective at producing remission in elderly patients with treatment-resistant depression (Lecrubier et al, 1997).

3. What factors influence dosage choice, duration of therapy and withdrawal requirements of antidepressants in the elderly?

The dosage choice (especially for TCAs) has historically been the one that has produced the fewest or least severe side-effects. However, this has also meant that subtherapeutic levels have resulted in the depression remaining untreated and becoming chronic in nature. Proponents for using TCAs as first-line treatment for depression in elderly people (Macdonald, 1997; Spigset and Mårtensson, 1999) give advice to 'start low and go slow'. Good advice, but it often means that the patient is inadequately treated for a greater period of time, which enhances the morbidity and mortality associated with depression in this age group. As an inpatient, TCAs can perhaps be increased in dose more quickly, as the patient is under close observation and debilitating and potentially life-threatening side-effects (postural hypotension and falls) can perhaps be pre-empted by physical support on standing and walking. Halving the normal maintenance dose of SSRIs on initiation for seven days can reduce associated anxiety, nausea and vomiting that may be associated with therapy

(De Vane and Pollock, 1999). As these side-effects generally disappear after five to seven days, this dose reduction can minimize further decreases in a patient's quality of life.

The time to therapeutic effect is delayed in the elderly and may take at least six to eight weeks before improvement is seen, with any pharmacological class (Paykel et al, 1995). Reasons for this phenomenon are unclear.

Previously, a response rate has been defined as a 50% improvement (from baseline score) in the Hamilton Rating Scale for Depression (HAMD) score or Geriatric Depression Scale (GDS), and this is seen in 50-60% of all treated patients. However, in the severely depressed this means that a patient is experiencing symptoms of depression and impairment of their normal life activities, and treatment should not perhaps be deemed to be successful until the scores do not depict a picture of depression. Then the treatment should be continued for a period of at least one year from complete symptom resolution.

The clinical implications of a partial remission in the elderly is an increased risk of relapse and early relapse, increased functional impairment, an increased suicide rate and an increased risk of chronicity of depression of perhaps 50%.

The recurrence rate on discontinuing antidepressants is high. Emerging research has shown that of those elderly patients with a first episode of depression who achieve symptom resolution after 2 years of treatment, 25% will relapse within two years of medication withdrawal (Flint and Rifat, 1999). Withdrawal of the antidepressant should be over at least four weeks, perhaps eight weeks, and the patient (and/or carers) need to be informed of the reason for this. There are now liquid formulations available which may ease the transitional period if withdrawal effects are seen with the shorter acting SSRIs such as paroxetine. Withdrawal effects seem to be less of a problem with fluoxetine probably because of its long half-life.

4. Discuss the various social issues that must be resolved before VF can be discharged home.

VF has several issues that will need resolving before her discharge. She is presently exhibiting bereavement grief, which may benefit from counselling

and cognitive behaviour therapy. She currently lives in a large family home in a fairly isolated area and does not want to return there alone. However, making a life-changing decision such as moving at this stage of her recovery is perhaps unwise. She should perhaps be discharged with a care package, which includes attendance at local day centres as appropriate, so that she may make the decision after a trial at home on her own. VF does not want to be a burden to her son and his partner and feels that she cannot stay with them for a prolonged period, although this is an option already put forward by her son. This feeling of low self-worth may change once her depression starts to resolve. The suicidal ideation needs to be monitored throughout treatment for her depression. Agoraphobia is common in the elderly after any life-changing event and VF will need careful supervision and monitoring to ensure that this is pre-empted.

5. What is the role of adjuvant medication such as benzodiazepines and hypnotics in treating the elderly depressed?

It is perhaps tempting to prescribe hypnotic and anxiolytic drugs to any depressed patient with increased agitation and anxiety. However, polypharmacy can lead to iatrogenic illness and precipitate delirium in this age group. The number of medicines should be kept to a minimum and benzodiazepines are best avoided where possible. Side-effects of benzodiazepines include cognitive impairment, memory loss, risk of dependence and increased risk of falls (all benzodiazepines have a relaxant effect on skeletal muscle). VF's anxiety should resolve as the depression starts to lift. Possible exacerbation of anxiety on initiation of SSRI treatment could be pre-empted by reducing the starting dose of the SSRI whilst educating the patient on relaxation and coping techniques.

The elderly are also very sensitive to the effects of hypnotics and where possible these should be avoided and good sleep hygiene patterns put in place. If hypnotics must be used then, to avoid tolerance and adverse effects, the lowest possible dose should be used, preferably on alternate nights and for the shortest possible period of time. The licensed starting dose for zopiclone in this age group is 3.75 mg. Side-effects include cognitive impairment, dizziness, dependence and coordination problems, all of which may decrease the patient's already poor quality of life.

All medication in the elderly needs regular, careful and judicial review to assess the need for continued prescribing.

Key points

- SSRIs and TCAs are equally efficacious at therapeutic doses in treating depression in the elderly.
- The choice of pharmacological agent is dependent on tolerability, toxicity, suicidal intent and cost.
- The low acquisition costs of TCAs are far outweighed by the increased need for dose titration and monitoring, adverse effects, iatrogenic illness, and hospitalization due to falls and fractures.
- The individual choice of an SSRI is dependent on patient factors including concomitant medication and pathology, pharmacokinetic changes and tolerance to adverse effects.
- The treatment of depression in the elderly needs to be holistic, with attention paid to social isolation, financial problems, possible bereavement and concomitant physical illness.

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Psychosis in the elderly

Denise Taylor

MH, an 82-year-old man, was admitted to hospital suffering from an acute psychotic episode. He had no previous documented admission/treatment for psychosis or other mental illness, but had a three-day history of increasing agitation and aggression, which included verbal abuse of his neighbours and home help.

MH believes that:

- *His neighbours were trying to poison him by piping poison down the chimney.*
- *He could hear his neighbours plotting to kill him when he listened at the wall.*
- *He could smell the poisonous gas creeping up the walls of the lounge.*

MH's current behaviour includes:

- *Shouting at his neighbours and threatening them with a broom when they come along the communal path.*

- *Banging on the adjoining wall to make the voices stop.*
- *Preventing the home help from entering the house, accusing her of spying 'and collaborating with the enemy'.*

On admission MH was verbally aggressive, resistive, agitated and pacing up and down. He lacked concentration and accused staff of trying to kill him by poisoning his tea. MH has a 15-year history of hypertension, is of frail build but is otherwise fairly mobile. Ward staff are requesting that risperidone be prescribed so that they can calm him down as he is upsetting other residents on the ward.

Medication on admission:

Bendrofluazide	2.5 mg mane (15 years)
Adalat LA (nifedipine)	30 mg mane (five years)

BP: 135/85 Pulse: 80

Questions

1. What differential diagnoses must be considered and excluded before any medication is prescribed and/or administered?
2. If a typical antipsychotic is to be administered, what are the cautions and contraindications for use in the elderly?
3. Discuss the merits of using atypical antipsychotics to treat psychosis in the elderly.
4. How should treatment with an antipsychotic be initiated and what is the optimum duration of treatment?
5. What non-pharmacological alternatives are there to modify MH's behaviour?

Answers

1. What differential diagnoses must be considered and excluded before any medication is prescribed and/or administered?

The prevalence of psychotic disorders in the elderly community population is about 1%. Acute transient psychotic episodes are rare. More common are persistent delusional disorders (late paraphrenia) or chronic schizophrenia

that persists into old age (Macdonald, 1997). It is imperative that a first episode of psychosis is thoroughly investigated before any formal diagnosis is made. The elderly suffer from greater co-morbidity than other age groups and there are many disease states that present with agitation and psychosis. Most commonly associated are dementia, depression and delirium (Bulow, 1999). The onset of dementia can be so insidious that it is not recognized by family or carers until a behavioural change highlights the possibility. A diagnosis of dementia requires a complete and thorough battery of cognitive testing according to local protocol.

Depression can often present with psychotic symptoms and behavioural changes in the elderly; therefore, depression assessment scales should be used to ensure that a readily treatable condition is not missed. Perhaps more likely though is an underlying delirium which may coexist with a depressive or dementing disorder. Delirium is extremely common in this age group affecting as many as 24% of all hospital admissions. There are many triggers for delirium, the most common being:

- **Infection** - especially urinary tract infections (UTIs) or lower respiratory tract infections (LRTIs). The elderly have a delayed immune response to infection and can become systemically very unwell before changes in X-rays, temperature, etc are seen.
- **Metabolic and endocrine disorders** - especially thyroid disorders and electrolyte disturbances.
- **Neurological disorders** - especially stroke and transient ischaemic attacks.
- **Cardiovascular disease** - especially heart failure (poor cerebral perfusion) and arrhythmias.
- **Medication toxicity** - this includes intoxication, withdrawal and drug side-effects.
- **Other medical conditions** - e.g. chronic constipation, chronic pain or urinary retention (Bulow, 1999; Targum and Abbott, 1999).

Potential causes for MH's current presentation include:

- Dementia (insidious onset that has not been noticed due to his relative social isolation).
- Depression [could be triggered by long-term use of Adalat LA

(nifedipine), a calcium-channel blocker which may cause or exacerbate depression]
- Delirium (he may have an infection, a metabolic disturbance from long-term diuretics or have suffered from a cerebrovascular event).

Therefore, the prescribing and administration of an antipsychotic should be withheld until MH has undergone a physical examination and any relevant investigations. The only exception is if his condition suddenly and seriously deteriorates and he becomes a danger to himself or other people on the unit. A dementing illness should be excluded if possible, as the anticholinergic side-effects of the antipsychotic agents are well known to impair cognitive function even further. Expressly, dementia with Lewy bodies must be excluded due to the increased risk of mortality when antipsychotics are administered to patients with this disorder (McKeith et al, 1992, 1995).

2. If a typical antipsychotic is to be administered, what are the cautions and contraindications for use in the elderly?

Typical antipsychotics are widely used and overprescribed in this age group (Hughes et al, 1999; Maixner et al, 1999) yet there are few studies which document the safety, efficacy and tolerability of these older agents. This overprescribing continues despite the growing evidence that these pharmacological agents are associated with exacerbating and precipitating cognitive impairment in this age group (McShane et al, 1997). The elderly are exceptionally sensitive to the side-effects of any medication, but especially to the histaminergic, adrenergic, muscarinic, cardiovascular and extrapyramidal side-effects (EPSEs) associated with the typical antipsychotics (Masand, 2000). The prevalence of tardive dyskinesia (TD) in this age group is five to six times greater than in younger ones (Jeste, 2000). TDs can appear after only one-month's treatment with a typical antipsychotic in patients older than 60 years who were previously neuroleptic-naïve. One study found the incidence of TD to be 3.4% at one month, 5.9% at three months, rising to 23% at 12 months (Jeste et al, 1995).

Age-related changes affect the pharmacokinetics and pharmacodynamics of the typical antipsychotics. The elderly have reduced lean body mass, with a corresponding increased lipophilic store and decreased serum albumin, all

of which affect the distribution and transportation of a pharmacological agent. The larger lipophilic stores mean that there is a correspondingly greater volume of distribution for lipid-soluble agents such as phenothiazines. Clinically, this means that when dosing with a lipophilic agent it may seem to take an unexpectedly long period of time before therapeutic effect is reached. This is because the agent is distributing throughout lipophilic stores before exerting an effect. Then it seems to overwhelm the patient with a corresponding prolonged effect as the agent leaches from lipophilic stores.

Ageing also results in decreased renal and hepatic mass (indeed, all organ mass and blood flow is reduced), which affects the body's ability to metabolize and then excrete medicines. Reduced first-pass effect of the liver can also lead to unpredictable increases in plasma levels of agents cleared in this manner. These changes can result in unpredictable and wide intersubject variation in plasma concentrations of these agents from the same dose (Maixner et al, 1999).

Organ sensitivity is also increased in the elderly and baroreceptor function is compromised, increasing sensitivity to the cholinergic and adrenergic side-effects of typical antipsychotics. These changes conspire to make the elderly more sensitive to the adverse effects of these agents, which can then be exhibited as an iatrogenic illness by the patient, e.g. parkinsonian symptoms, postural hypotension, hypo- or hyperthermia, syncope or an apparent worsening of psychosis due to akathisia. Iatrogenic illness is a major cause of morbidity and mortality in the elderly and has a profound negative effect on a patient's health-related quality of life.

The Omnibus Budget Reconciliation Act (OBRA) legislation introduced in the USA (Hughes et al, 1999; Maixner et al, 1999), which restricted the prescribing of these agents in elderly people due to their deleterious effect on cognitive function and mortality, should be seen as the means to modernize antipsychotic prescribing in this very vulnerable patient group in the UK, i.e. typical antipsychotics should no longer be typically prescribed.

3. Discuss the merits of using atypical antipsychotics to treat psychosis in the elderly.

The newer or atypical antipsychotics offer a safer and equi-efficacious

alternative to the older antipsychotic agents with increased patient tolerability due to their increased specificity at serotonergic and dopaminergic binding sites at low dose. They are still associated with side-effects but generally these are experienced at higher dose ranges. However, it must be noted that due to the pharmacokinetic changes in this age group, higher plasma concentrations will be reached using much lower doses than in younger patients. Increasingly, studies in this age group are demonstrating symptom control using 1 mg risperidone as a total daily dose, with increasing side-effects (EPSEs and postural hypotension) at doses >2 mg daily (Katze et al, 1999). Risperidone does not reduce the seizure threshold, block histamine receptors and has no anticholinergic side-effects. Indeed, one study of elderly patients taking risperidone for psychosis demonstrated an improvement in cognition over the treatment period (Jeste et al, 1996). If started at a dose of 500 micrograms daily (usually at night) and then increased in daily increments of 500 micrograms (as a twice daily dosing regimen), then the risks of postural hypotension can also be minimised (Kumar and Brecher, 1999).

Clozapine has an increasing evidence base for its use in the elderly, but due to its extensive monitoring requirements and the increased sensitivity of the elderly to the development of neutropenia, it is not an agent that should be used as a first-line treatment in this age group (Maixner et al, 1999). Indeed, its licence precludes its use.

Unpublished data from phase II/III clinical trials demonstrates that quetiapine is well tolerated in the elderly, with an adverse event profile similar to that seen in younger patients (Dev and Raniwalla, 2000). It is associated with a low incidence of seizures; the incidence of sedative effects are similar to those seen with chlorpromazine, although postural hypotension can be a problem if titration is too rapid. Again, its lack of anticholinergic activity is an advantage for its use in the elderly. However, clearance rates are reduced (30–50%) and therefore lower doses reach higher plasma concentrations. It is recommended that dosing is started at 25 mg once daily, increasing by 25 mg increments every one to three days until therapeutic effect is reached (Dev and Raniwalla, 2000). QTc prolongation has been reported with quetiapine and

therefore this agent should not be used as a first-line treatment in patients with a history of cardiovascular disease or arrhythmia, or in conjunction with other medicines that may prolong the QT interval (Dev and Raniwalla, 2000; Czekalla et al, 2001).

Olanzapine has been used extensively for the treatment of psychoses in the elderly. There is evidence to suggest that it is as effective as haloperidol without inducing EPSEs at therapeutic doses (note that this will be lower in the elderly due to reduced clearance). In comparison with risperidone, fewer EPSEs have been reported, but there is an important incidence of drowsiness, anticholinergic effects and weight gain. Initial dosing of 2.5–5 mg in the elderly can help avoid postural hypotension. A starting dose of 5 mg should be used in any patient with hepatic or renal impairment (Anon, 1997). It should be noted that all elderly patients should be assumed to have at least mild renal impairment.

4. How should treatment with an antipsychotic be initiated and what is the optimum duration of treatment?

Any antipsychotic needs to be started at a dose which is at least one-half of the recommended starting dose in younger patients. Patients with Lewy body dementia are extremely sensitive to any antipsychotic and their use is not justified except in extreme circumstance. On these rare occasions, doses as little as one-quarter of the recommended starting dose are advised, with close observation of the patient for deleterious effect. Once initiated, the dose should be slowly titrated against therapeutic effect and thereafter reviewed at least fortnightly for continued need. The patient should be observed for the presence of adverse events on at least a daily basis, with dose adjustments made as necessary. It is also advised that patients receive regular heart rate and blood pressure monitoring throughout titration and after every dose change.

Withdrawal of the agent should be over at least one to two weeks (longer if long-term therapy is being withdrawn) with close patient observation for discontinuation effects.

The reader is reminded that in neuro-degenerative disease, the behaviour will change as the disease progresses, therefore continued medication is often unnecessary.

5. What non-pharmacological alternatives are there to modify MH's behaviour?

Where possible, non-pharmacological methods should be employed to treat behavioural disturbances in this age group. Patients who have poor concentration are often easily distracted and behavioural intervention methods are recommended (Alexopoulos et al, 1998; SIGN, 1998; Ballard and O'Brien, 1999). These include:

- Creating an environment which is calming.
- Providing activities to reduce boredom and loneliness.
- Providing a regular routine.
- Providing pro-active non-confrontational patient care.
- Ensuring that the physical environment is optimum, i.e. temperature control, space to walk.
- Other psychological strategies include the **ABC analysis**. The patient is carefully observed over a two-week period for the following:
    - **Antecedents** to behavioural disturbance, e.g. television programmes, meal times, nurse of the opposite sex involved in bathing routine.
    - **Behaviour** - clear description of the behaviour exhibited.
    - **Consequences** - if the consequence is unimportant, does the behaviour require treatment?

OBRA recommendations include that behaviour is observed for up to one month in patients with neuro-degenerative disease before any pharmacological treatment is initiated (Alexopoulis et al, 1998; SIGN, 1998; Ballard and O'Brien, 1999; Maixner et al, 1999). This is to ensure that the behaviour is not just a short-term manifestation of disease progression. Unnecessary medication puts the elderly patient at risk of increased morbidity and mortality by possible precipitation of iatrogenic illness. All medication should be frequently and judicially reviewed to ensure that continuing need is absolutely necessary.

Key points

- A full assessment is required before any antipsychotic is prescribed and/or administered.
- The elderly are at increased risk of developing permanent and disabling EPSEs and worsening cognitive function with the typical antipsychotics at any dosage used.

- **The atypical antipsychotics offer an alternative: they have fewer neurological side-effects but can cause other side-effects, which vary with individual drugs.**
- **Non-pharmacological treatments should always be attempted for the management of behavioural disturbance in the elderly before antipsychotics are prescribed.**

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26

Alzheimer's disease

David Taylor

ZD, a 72-year-old retired engineer, is seen in outpatients with his wife having been referred by his GP following several episodes where ZD had become lost while out of the house on errands.

ZD is well dressed but quiet and withdrawn. His wife reports that he has become quite miserable in the past few weeks. ZD denies any problems with his memory but admits to feeling depressed.

A mini-mental state examination (MMSE) is performed and ZD scores 24 out of a possible 30. His main deficits are in orientation in time and place. After further tests are performed and reported upon, ZD is, at his next appointment, given a provisional diagnosis of Alzheimer's disease.

Questions

1. How might cholinesterase inhibitors help ZD?
2. Are there clinically relevant differences between available cholinesterase inhibitors?
3. Outline a protocol for the drug treatment of Alzheimer's disease.
4. Which antidepressants might be suitable for ZD?

Answers

1. How might cholinesterase inhibitors help ZD?

Four compounds are currently licensed for the treatment of Alzheimer's disease (tacrine, donepezil, rivastigmine, galantamine) and all inhibit acetylcholinesterase. Tacrine is very poorly tolerated and has been superseded by the other three drugs: it will not be discussed further. Cholinesterase inhibitors differ in pharmacological action: donepezil and galantamine are selective inhibitors of acetylcholinesterase (AChE); rivastigmine affects both AChE and butyrylcholinesterase (BuChE); donepezil and rivastigmine are relatively selective for AChE in the brain; galantamine also affects nicotinic receptors (Weinstock, 1999). So far, these differences have not been shown to result in differences in efficacy or tolerability.

All three drugs seem to have broadly similar clinical effects, as measured using the mini-mental state examination (MMSE; a 30-point, basic evaluation of cognitive function) and the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog: a 70-point evaluation largely of cognitive dysfunction). Major trials of anticholinesterases are summarized in Table 28.1.

The results shown in Table 28.1 need to be interpreted with caution. Alzheimer's disease is usually characterized by inexorable cognitive decline, which is generally well quantified by tests such as ADAS-cog and MMSE. The average rate of decline is four to six points on the ADAS-cog over one year, but the range is large. It is therefore difficult to

assess accurately treatment effect in individual patients. The effect of anticholinesterases is, on average, to improve modestly cognitive function for several months (scores return to baseline after about nine to 12 months (Rogers and Friedhoff, 1998; Raskind et al, 2000). This average incorporates and, to some extent, conceals three groups of patients: non-responders, who continue to decline at the anticipated rate; non-decliners, who neither improve significantly nor decline, and improvers, who improve to a clinically relevant extent. This last group is usually defined as those who show a greater than four-point improvement on ADAS-cog. In trials of around six months, approximately 25–35% of those on anticholinesterases will be classified as 'improvers' compared with around 15–25% on placebo (see Table 28.1). Around 55–70% of patients treated with anticholinesterases will show no cognitive decline during a five- or six-month trial (Rösler et al, 1999; Raskind et al, 2000), about 20% more patients in absolute terms than those on placebo. Note that both the mean change in cognitive function scores and the proportion of patients improving decrease in trials of longer length (which allow a longer time for disease progression). Note also that, for the most part, results of trials so far conducted relate only to patients with mild to moderate Alzheimer's disease (those giving a score of 10 to 26 on MMSE).

In general, in a cohort of patients given anticholinesterases at optimal doses under clinical trial conditions, approximately one-third would be expected to improve over six months and around another one-third would be expected not to deteriorate.

2. Are there clinically relevant differences between available cholinesterase inhibitors?

Few important differences have been noted in pre-clinical studies, clinical trials or clinical practice. There are, however, some pharmacological differences between drugs which may eventually be seen to translate into important clinical differences. For example, rivastigmine affects both AChE and BuChE. In healthy adults, BuChE is concentrated in peripheral tissues, but in late-stage Alzheimer's disease cholinergic neurones are replaced by glia and glia contain BuChE. It is possible, in theory, that rivastigmine may show superior efficacy in the late stages of Alzheimer's disease.

Table 28.1
Placebo-controlled trials of cholinesterase inhibitors

Reference	*Drug and dose*	*n*	*Duration*
Rogers et al (1998a)	Donepezil 5 mg Donepezil 10 mg	468	12 weeks
Rogers et al (1998b)	Donepezil 5 mg Donepezil 10 mg	473	24 weeks
Rogers and Friedhoff (1998)	Donepezil up to 10 mg	133	Up to 192 weeks
Corey-Bloom et al (1998)	Rivastigmine 1–4 mg Rivastigmine 6–12 mg	699	26 weeks
Rösler et al (1999)	Rivastigmine 1–4 mg Rivastigmine 6–12 mg	725	26 weeks
Tariot et al (2000)	Galantamine 8 mg Galantamine 16 mg Galantamine 24 mg	978	Five months
Raskind et al (2000)	Galantamine 24 mg Galantamine 32 mg	636	Six months
Wilcock et al (2000)	Galantamine 24 mg Galantamine 32 mg	653	Six months

ADAS-cog change versus placebo	*MMSE versus placebo*	*Proportion of points showing > 4 point change in ADAS-cog*	*Approximate number needed to treat (NNT) (most effective dose)*
2.5 (5 mg) 3.1 (10 mg)	1.0 (5 mg) 1.3 (10 mg)	Not given, but improvement seen in 38% (10 mg), 32% (5 mg) and 18% (placebo)	**5**
2.5 (5 mg) 2.9 (10 mg)	1.2 (5 mg) 1.4 (10 mg)	38% (5 mg) 54% (10 mg) 27% (placebo)	**4**
Scores improve then cross baseline at 38 weeks (no placebo)	Not given	Not applicable	–
4.9 (6–12 mg) *(lower doses not active)*	1.1 (6–12 mg)	25% (6–12 mg) (placebo results not given)	Not possible to calculate
2.6 (6–12 mg) *(lower doses not active)*	Not given	24% (6–12 mg) 16% (placebo)	**12**
3.3 (16 mg) 3.6 (24 mg)	Not given	36% (16 mg) 37% (24 mg) 20% (placebo)	**6**
3.9 (24 mg) 3.8 (32 mg)	Not given	33% (24 mg) 34% (32 mg) 17% (placebo)	**6**
2.9 (24 mg) 3.1 (32 mg)	Not given	29% (24 mg) 32% (32 mg) 15% (placebo)	**6**

All available anticholinesterases have shown broadly similar efficacy against cognitive symptoms in clinical trials (Table 28.1). Any minor differences observed may be accounted for by differences in trial design or patient characteristics. In the absence of any head-to-head studies, the available drugs should be assumed to have equal efficacy.

Anticholinesterases may also affect non-cognitive aspects of Alzheimer's disease. For example, they seem to have useful psychotropic activity against neuropsychiatric symptoms (Blesa, 2000; Cummings and Askin-Edgar, 2000; Weiner et al, 2000). These drugs may also lower care-giver burden (Gauthier et al, 1999) and improve patients' abilities with daily activities (Winblad et al, 1999). Differential effects for different drugs have yet to be demonstrated.

Drug tolerability may differ between anticholinesterases but, again, in the absence of direct comparisons, it is difficult to draw cogent conclusions. Overall tolerability can be broadly evaluated by reference to numbers withdrawing from clinical trials (Table 28.2). Tolerability seems to be affected by speed of titration and, perhaps less clearly, by dose. Most adverse effects occurred in trials during titration and slower titration schedules are recommended in clinical use. This may mean that these drugs are equally well tolerated in practice.

The different titration schedules do, to some extent, differentiate anticholinesterases. Donepezil is easiest to use, starting at 5 mg daily and increasing, if necessary (however this might be determined), to 10 mg daily after one month. Rivastigmine is taken twice daily, starting at 1.5 mg BD, increasing to 3 mg BD after two weeks or more and then to 4.5 mg BD after a further two weeks (maximum 6 mg BD). With galantamine, the starting dose is 4 mg twice daily, increasing to 8 mg twice daily after four weeks and then to 12 mg BD, if necessary, four weeks later. Thus, both rivastigmine and galantamine need to be given twice daily and have prolonged titration schedules. These factors may be important to prescribers, patients and carers.

Potential for interaction may also differentiate currently available cholinesterase inhibitors. Donepezil (Dooley and Lamb, 2000) and galantamine (Scott and Goa, 2000) are metabolized by cytochromes 2D6 and

Table 28.2
Adverse effects of anticholinesterases

Reference	Drug and dose	n	Withdrawals due to adverse effects	Most frequent adverse effects reported
Rogers et al (1998a)	Donepezil 5 mg Donepezil 10 mg	468	Placebo 1% 5 mg 4% 10 mg 9%	Nausea Insomnia
Rogers et al (1998b)	Donepezil 5 mg Donepezil 10 mg	473	Placebo 7% 5 mg 6% 10 mg 16%	Diarrhoea Nausea
Corey-Bloom et al (1998)	Rivastigmine 1–4 mg Rivastigmine 6–12 mg	699	Placebo 7% 1–4 mg 8% 6–12 mg 29%	Nausea Dizziness
Rösler et al (1999)	Rivastigmine 1–4 mg Rivastigmine 6–12 mg	725	Placebo 7% 1–4 mg 7% 6–12 mg 23%	Nausea Vomiting
Tariot et al (2000)	Galantamine 8 mg Galantamine 16 mg Galantamine 24 mg	978	Placebo 7% 16 mg 7% 24 mg 10%	Nausea Vomiting
Raskind et al (2000)	Galantamine 24 mg Galantamine 32 mg	636	Placebo 8% 24 mg 23% 32 mg 32%	Nausea Vomiting
Wilcock et al (2000)	Galantamine 24 mg Galantamine 32 mg	653	Placebo 9% 24 mg 14% 32 mg 22%	Nausea Vomiting

3A4, and so drug levels may be altered by other drugs affecting the function of these enzymes. Also, anticholinesterases themselves may interfere with the metabolism of other drugs, although this is perhaps a theoretical consideration. Rivastigmine has almost no potential for interaction since it is metabolized at the site of action and does not affect hepatic cytochromes. Overall, rivastigmine appears to be least likely to cause problematic drug

interactions, a factor which may be important in an elderly population subject to polypharmacy.

When adverse effects occur, they are largely predictable: excess cholinergic stimulation leads to nausea, vomiting, dizziness, insomnia and diarrhoea (Dunn et al, 2000). Urinary incontinence has also been reported (Hashimoto et al, 2000). There appear to be no important differences between drugs in respect to type or frequency of adverse events, although clinical trials do suggest relatively lower frequency of adverse events for donepezil (see Table 28.2).

3. Outline a protocol for the drug treatment of Alzheimer's disease.

A number of protocols for the use of anticholinesterases have been produced (eg Taylor et al, 2000) and are widely used to ensure good-quality prescribing (Taylor et al, 2001). Broadly speaking, any protocol should ensure that only specialists assess suitability for anticholinesterases (usually those patients with mild to moderate Alzheimer's disease) and monitor patients to identify those who are benefiting from the drug prescribed. Benefit is usually defined as clear arresting of deterioration or an improvement in cognitive function, measured using MMSE (NICE, 2001). Those patients not benefiting after three to six months are usually withdrawn from treatment. Those responding should be monitored every three months to assure continued benefit is being gained.

Using a protocol like this may mean that, of a cohort of patients referred for treatment, only three-quarters may be considered suitable for treatment and only one-third of those starting may continue treatment for one year or more (Matthews et al, 2000). In contrast, in the artificial environment of a clinical trial, nearly half of patients continued for two years or more (Ieni et al, 1999).

4. Which antidepressants might be suitable for ZD?

Alzheimer's disease is often accompanied by depression, especially in the early stages of the illness. Its treatment is empirical, since few, if any, studies have sought to establish the relative worth of different antidepressants in Alzheimer's disease.

It is important to avoid drugs which may worsen memory loss, specifically drugs with anticholinergic activity. All

tricyclic antidepressants have anticholinergic properties, as do, to a lesser extent, paroxetine and mirtazapine. Sedative drugs may also worsen cognitive function, but may be helpful where there is nighttime behavioural disturbance. For this reason, trazodone is quite widely used, although its effect on blood pressure can be troublesome. Benzodiazepines may be helpful, but they too can affect short-term memory and cause confusion and falls.

For ZD, selective serotonin reuptake inhibitors may be used, as may reboxetine, moclobemide and venlafaxine.

Key points

- Cholinesterase inhibitors have pharmacological differences which have yet to be reflected in clinical trial results.
- Cholinesterase inhibitors bring about improvement in around one-third of patients.
- Adverse effects include nausea, vomiting, dizziness and insomnia.
- Donepezil may be better tolerated than other cholinesterases and has the simplest dosage regimen.

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27

Use of atypical antipsychotics to treat behavioural symptoms of dementia

Anne Connolly

BM, a 78-year-old Caucasian man, was admitted to a care of the elderly ward after biting his elderly wife's arm. On interview, BM's wife revealed that this incident was the culmination of a gradual and distressing change in her husband's behaviour. This included persistent swearing such that she was embarrassed to go to the local day centre; restlessness and wandering at night leaving them both exhausted; repeatedly removing his clothing and then putting it all back on again; eating food only using a teaspoon. Often he would become apathetic and withdrawn. She wept openly when describing her husband's behaviour and said her home life had become a 'living nightmare'.

BM has a two-year history of dementia and his current medication is donepezil 10 mg daily and trazodone 150 mg at night. Since admission he has tried repeatedly to leave the ward saying he wanted to go home to Paris (where he lived five

years ago) and on one occasion threw a fire extinguisher through a glass window. His wife remains in hospital recovering from her injuries.

Questions

1. What are behavioural symptoms of dementia (BSD)?
2. How are BSD treated?
3. Which atypical antipsychotic could be used to treat BM?
4. BM is prescribed risperidone but refuses it. What practical and ethical difficulties are there in administering medication to patients with dementia?

Answers

1. What are behavioural symptoms of dementia (BSD)?

Unfortunately, there is still no international agreement of the description and definition of BSD (Frenchman and Prince, 1997; Stoppe et al, 1999), mainly because symptoms do not fit into a recognized psychiatric disorder but include those from many different illnesses. Difficulties defining BSD are further compounded by problems in measuring them objectively because of the lack of a standardized rating scale (Shah and Allen, 1999).

Symptoms can be divided into those that are and those that are not psychotic. Psychotic features include delusions and hallucinations whilst non-psychotic features are often referred to simply as 'agitation' (Small et al, 1997). Agitation has been described as inappropriate verbal, vocal or motor activity unexplained by apparent needs or confusion, and may eventually occur in approximately half of all patients with dementia (Rapp et al, 1992; Tariot, 1999). Agitation may include any of the following symptoms:

- Verbal – complaints, requests for attention, verbal outbursts, shouting, screaming, threats, accusations, name-calling, obscenities, rage, anger.
- Physical/motor – restlessness,

pacing, wandering (especially at night, known as 'sundowning'), fidgeting, hand wringing, compulsive ritualistic behaviour, incontinence, pulling clothes, inappropriately dressing and undressing, abnormal eating behaviour, hitting, pushing, biting, scratching, kicking, uncooperativeness, violence, demanding or critical behaviour, physical resistance.

- Other - antisocial behaviour, sexual aggression, hypersexuality, self-harm, apathy, withdrawal.

See Rapp et al (1992), Patel and Hope (1993), Herrmann et al (1996), Borsond and Raskind (1997), Class et al (1997), Grossman (1998), and Tariot (1999) for more details.

BM's behavioural symptoms include some from each category; verbal (persistent swearing); physical (biting his wife's arm, wandering at night, repeatedly dressing and undressing); apathy and withdrawal. Behavioural symptoms can be more problematic and distressing than cognitive symptoms, especially for carers. Ultimately, they can lead to nursing home or hospital admission (Tariot, 1999).

Aggressive behaviour in dementia is known to be associated with depression (Lyketsos et al, 1999). BM is receiving trazodone, although it is unclear if it was originally prescribed to treat depression or BSD. Depression should be excluded as a potential cause of BM's behaviour.

2. How are BSD treated?

Many drug treatments have been tried for BSD. These include selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, cholinesterase inhibitors and trazodone. The role of cholinesterase inhibitors in treating BSD is being investigated and the data so far are cautiously encouraging (Cummings, 2000; Weiner et al, 2000). There is some evidence that cholinergic deficits contribute to BSD and that treatment with cholinesterase inhibitors can reduce behaviours such as uncooperativeness, agitation, anxiety, apathy, depression, delusions and hallucinations (Cummings, 2000). BM is already receiving donepezil 10 mg daily, the maximum licensed dose. Consideration may be given to switching BM to an alternative cholinesterase inhibitor as there are subtle, but potentially important, differences in the pharmacological profiles of individual drugs. BM should

also be assessed for the presence of depression and his antidepressant dose increased or an alternative prescribed if indicated.

Antipsychotics have been studied in the treatment of BSD (Stoppe et al, 1999), with typical antipsychotics often cited as a standard treatment (Pollock and Mulsant, 1998). Use of typical antipsychotics in nursing-home patients is controversial. There is concern that they have been used as 'chemical restraints', effectively replacing nursing care. This has led to legislation [Omnibus Budget Reconciliation Act of 1987 (OBRA '87)] in the USA which specifies when antipsychotics can and cannot be used to treat behavioural disturbances in nursing-home patients. In addition, medical and nursing staff have been reported to have low expectations of efficacy of antipsychotics in treating BSD (Thacker, 1996), particularly for resistive and sexually inappropriate behaviour.

Typical antipsychotics are of limited efficacy in treating BSD and their use is associated with extra-pyramidal side-effects (EPSEs) and further cognitive impairment. Both can be detrimental to the patient's quality of life (Borsond and Raskind, 1997; Tariot, 1999). BM's dementia type is not specified but patients with dementia with Lewy bodies (DLB) are extremely sensitive to the side-effects of antipsychotics, particularly EPSEs, sedation and anticholinergic effects. Fatal antipsychotic sensitivity reactions have been reported (Ballard et al, 1998). In all dementias, anticholinergic side-effects are relatively more important than in younger, healthier subjects. This is because central anticholinergic activity adversely effects cognitive function which may not be noticeable in younger people but can be catastrophic in patients with dementia. Antipsychotic drugs have been associated with an increased rate of cognitive decline in dementia patients (McShane et al, 1997), although it is unclear if the symptoms that prompt antipsychotic treatment are a poor prognostic factor or if the treatment for these symptoms is responsible. EPSEs can lead to falls and compound problems with mobility and dexterity.

Atypical antipsychotics by definition are less likely to cause EPSEs. However, one placebo-controlled trial found that one in five elderly patients treated with risperidone 2 mg daily experienced EPSEs, and one in four patients

experienced somnolence or falls (Katz et al, 1999).

3. Which atypical antipsychotic could be used to treat BM?

It is difficult to be certain of efficacy and tolerability with atypical antipsychotics in BSD given the small sample sizes, high placebo response rates, lack of randomized placebo-controlled trials and the open-label, case-study nature of much of the data. Moreover, efficacy should not be readily assumed, especially when one considers the reputation of typical drugs in this area is based rather more on anecdote than on cogent trial data. Encouraging outcomes with atypical antipsychotics are usually reported when treating general BSD rather than specific symptoms, e.g. self-injurious behaviour. Atypical antipsychotics appear to be better tolerated in elderly patients as they cause fewer EPSEs and less tardive dyskinesia (TD) than typical antipsychotics; however, clinically significant side-effects can, and do, occur.

Risperidone is the most studied of the atypical antipsychotics for BSD. If an atypical is to be used for BM then risperidone might be an appropriate choice (Frenchman and Prince, 1997; Herrmann et al, 1998; Irizarry et al, 1999; Katz et al, 1999). The safety of risperidone in DLB is unclear, with some authors describing case reports of safe and effective use (Allen et al, 1995) whilst others report fatal antipsychotic sensitivity reactions (Ballard et al, 1998).

Doses of risperidone used for behavioural symptoms are usually 0.5–2 mg daily (Tariot et al, 1997; Herrmann et al, 1998; Zayas and Grossberg, 1998; Stoppe et al, 1999; Defillippi and Crismon, 2000). Some authors suggest starting at doses as low as 0.25 mg daily (Jeste et al, 1996; Stoppe et al, 1999) and increasing slowly by no more than 0.5 mg daily (Jeste et al, 1996; Zayas and Grossberg, 1998). A double-blind trial found the incidence of EPSEs to be 21% and somnolence 28% at a dose of 2 mg risperidone daily (Katz et al, 1999).

Information on the use of **olanzapine** for BSD is more limited. Most of the data available relate to either the use of olanzapine as an antipsychotic in patients with dementia (Aarsland et al, 1999) or for the treatment of psychosis and behavioural disturbance (Street et al, 2000). Although olanzapine has been shown to be effective in treating psychosis in this patient group, there

are too few data to support the efficacy of olanzapine for behavioural symptoms alone in dementia. Street et al (2000) found minimal EPSEs in the elderly demented patient but the incidence of somnolence was 25–36% depending on the dose used.

There are two open-label trials that examine the efficacy of quetiapine in the elderly. Some of the subjects had psychotic symptoms in the context of dementia (McManus et al, 1999). As with olanzapine, the incidence of EPSEs was very low. Other significant side-effects did occur: somnolence in 32%, dizziness in 14% and postural hypotension in 13%. Further, more specific data are needed to evaluate the safety and efficacy of quetiapine for BSD.

It must be remembered that BSD are often time-limited (Hope et al, 1999) and that ongoing clinical review to assess the efficacy and side-effects of antipsychotic drugs is essential. The principles of OBRA '87 should be adhered to.

In summary, early impressions of the atypical antipsychotics risperidone, olanzapine and quetiapine are encouraging. However, further comparative trials are needed for firm conclusions to be reached on their place in the treatment of BSD.

4. BM is prescribed risperidone but refuses it. What practical and ethical difficulties may occur when administering medication to patients with dementia?

Administration of medication to patients with dementia who cannot consent to treatment is a frequently encountered problem. Patients with dementia are not detained under the Mental Health Act but are mentally incapacitated. Concealing medication in patients' food is a common practice, with a study by Treloar et al (2001) finding it occurred in 79% of long-stay elderly care facilities. They also suggest that 94% of carers of patients with dementia considered the practice legitimate in extreme circumstances. The deceiving of BM may increase the risk of abuse by health-care professionals. However, if BM is unable to make an informed choice to take medication then this may result in harm to himself or others. Refusal may provoke health-care professionals to assume that the patient has chosen to be harmed. Ethical opinion sides with the administration of medication in the least distressing manner, although some patient groups may oppose this view. Not enforcing the taking of medication may result in

unnecessary suffering for BM or his family. Behavioural disturbance leading to restraint and the use of injectable medication may be more than likely.

Secrecy surrounding this issue results in an increased risk of abuse, and a lack of safeguards and guidelines for good practice. Advance directives may help with the problem of consent, although most directives are written to prevent treatment. Readers are directed to the work of Hughes (2000) and Post (2000) for further information on the ethics of dementia care.

So, what practical steps can be taken to ensure BM takes the medication prescribed for him? First of all, it must be clear that BM is indeed incapacitated. If not, the Mental Health Act should be used. Using a liquid preparation, taking time and effort to persuade and work with BM, obtaining consent from his wife and, finally, concealing medication in food are all options. Any attempt to conceal medication in food should be fully discussed with the multidisciplinary team and the relatives. The decision, with a full risk-benefit analysis, should be documented in the patient's notes. The process should be open to prevent abuse. Concealing medication in food is a very last resort.

Key points

- Behavioural symptoms can be more problematic than cognitive symptoms for carers and often lead to nursing home or hospital admission.
- There is no international agreement of the description and definition of BSD.
- Typical antipsychotics are moderately effective in treating BSD but their use is limited by side-effects and poor tolerability, specifically EPSEs and cognitive impairment.
- Data on efficacy of atypical antipsychotics for BSD appears favourable, particularly when treating general rather than specific symptoms.
- Atypical antipsychotics are better tolerated in the elderly and cause fewer EPSEs and less TD than typical antipsychotics.
- Risperidone is the most studied of the atypical antipsychotics in BSD and if an atypical antipsychotic is to be used then the majority of data support the use of risperidone at low doses.
- Atypical antipsychotics should be used with extreme caution in

patients with DLB because fatal hypersensitivity reactions have been reported. Typical drugs are contra-indicated

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28

Self-injurious behaviour and learning disabilities

David Branford

KH is a 30-year-old severely learning-disabled woman. She is the youngest of three children. Both her brother and sister are of normal intelligence and free from any mental illness. The cause of KH's learning disability is unknown. From an early age KH showed autistic behaviours and was diagnosed as suffering from childhood autism. She suffered a first seizure at the age of 11 and a second, which may have been secondary to high lithium levels, at the age of 15.

The following are a series of situations that have occurred with KH over the years.

At the age of 14 KH was admitted permanently to hospital. Her behaviour had dramatically deteriorated following a series of changes at home and attempts at short-term breaks in hospital. She was biting herself and others, ripping her clothes and bedding and banging her head repeatedly. She was receiving carbamazepine 200 mg twice daily at this time.

Since admission to hospital KH has remained difficult to control. Her self-injurious behaviours continue to be extreme in severity. Repeated attempts at short-term breaks failed and her parents did not feel they could cope with her any more. Treatment with an increased dose of carbamazepine did not bring any benefit, and large doses of chlorpromazine resulted only in short-term drowsiness. Ten years on, KH still presents with a wide variety of self-injurious and destructive behaviours. These include: biting herself mostly on her shoulders and knee, slapping herself, pulling her own hair and banging her head. Occasionally she will bite others, attempt to pull their fingers back, obsessionally put her head down the toilet or attempt to flush her clothes down the toilet, scream, smash windows using her hand or head and deliberately urinate in bed. Throughout this period she has remained on carbamazepine 300 mg bd, lithium carbonate 500 mg bd and fluctuating doses of chlorpromazine. At one point, when these behaviours were at their most severe, chlorpromazine was prescribed at a dose of 1 g daily.

Physical examination revealed significant scarring to many areas of the body. Full blood count, thyroid function and urea and electrolyte tests were unremarkable, although both a tremor and an orofacial dyskinesia were evident. Her serum lithium level was 0.9 mmol/l.

The EEG report states:

> The record contains a fair amount of alpha activity at 8–9 Hz, 20–50 μV reactive and symmetrical. A fair amount of theta activity is present at 20–24 Hz, up to 35 μV intermixed and superimposed. No focal activity is found.
> Conclusion: The background is mildly abnormal. There are no focal/paroxysmal features seen.

Questions

1. What possible psychological, social and biological theories could explain the continued self-injury?
2. Give the arguments for and against the continuation of the carbamazepine.
3. Give the arguments for and against the continuation of the lithium carbonate.
4. Give the arguments for and against the continued prescribing of an antipsychotic drug.
5. What alternative drug therapies may be of benefit?

Answers

1. What possible psychological, social and biological theories could explain the continued self-injury?

Self-injurious behaviour (SIB) is a devastating and chronic problem which, although not exclusively confined to people with learning disabilities, presents a particular problem with this population (Reid and Ballinger, 1995; Read, 1998). Very little is known about the early stages of SIB in young children with learning disabilities (Murphy et al, 1999).

There is no clear understanding of the aetiology of SIB. Learning theories postulate that the behaviour may be reinforced by rewards such as attention or avoidance, and started by response to an event such as pain, menstruation, level of stimulation or mental illness.

Animal models suggest that SIB may have a biological cause. These include dopamine dysfunction particularly associated with D1 receptors (Breese et al, 1995; Schroeder et al, 1995) and opiate system dysfunction resulting in elevated levels of beta-endorphin. It has been suggested that the latter may be analogous to an addiction (Sandman and Hetrick, 1995).

2. Give the arguments for and against the continuation of the carbamazepine.

The following questions are relevant to the continuation of carbamazepine, lithium or antipsychotic drugs:

- Is the medicine indicated?

- Is there any evidence that it has been of value?
- Is the patient suffering from any adverse effects?
- Are withdrawal problems likely?

Is carbamazepine indicated? There are two issues to consider: firstly, is carbamazepine indicated for SIB and, secondly, is the patient suffering from active epilepsy? Much of the scarce evidence to support the use of carbamazepine for SIB is equivocal. For example, Barrett et al (1988) reported the use of carbamazepine in an 11-year-old girl with mild learning disabilities and epilepsy and found that, although self-injury, growling noises and facial grimacing were reduced, other unacceptable maladaptive behaviours were not. The second issue of whether antiepileptic drug treatment remains indicated for a person with severe learning disabilities when there has been no record of seizures for over 10 years remains difficult. The EEG result supports the decision to withdraw the carbamazepine. Also, there is not really any evidence that the carbamazepine has been of value.

Carbamazepine is associated with many side-effects including nausea, ataxia and drowsiness.

Although there is no withdrawal syndrome associated with carbamazepine, withdrawal may present a problem, particularly as KH has received the drug for many years. A slow programme of gradual withdrawal over a three- to six-month period should be recommended.

3. Give the arguments for and against the continuation of the lithium carbonate.

Is lithium indicated? The literature to support the use of lithium to treat aggression, self-mutilation and affective disorders in the context of learning disabilities was reviewed by Johnson (1988), who found the literature to be scant. In two large clinical trials (Tyrer et al, 1984; Craft et al, 1987) no clear opinion on the value of lithium treatment for SIB was developed. Most of the papers to support the efficacy of lithium were open trials involving small numbers of patients. For example, Micev and Lynch (1974) had earlier found that lithium produced complete elimination of SIB in six of eight self-mutilating patients. The literature to support the use of lithium for affective disorders is large but there is no indication in this case that the patient is suffering from an affective disorder.

There is no evidence that lithium has been of any value in this patient. The treatment has continued for almost 10 years, during which time the SIB has remained similar in frequency and severity. KH has received an adequate dose and there is some evidence that she is suffering from side-effects, notably tremor.

Although there are not usually any withdrawal effects associated with the use of lithium in SIB, it would be advisable to reduce the dose slowly over a three-month period.

4. Give the arguments for and against the continued prescribing of an antipsychotic drug.

Antipsychotic drugs have historically been the drugs most widely prescribed for SIB, although the evidence to support their efficacy is largely anecdotal. Systematic reviews have failed to provide evidence to support their efficacy (Brylewski and Duggan, 1999). The suggestion that SIB can be more effectively treated by antipsychotic drugs which have a high affinity for the dopamine D1 receptor rather than dopamine D2 was first proposed by Breese et al (1990) and subsequently tested by Schroeder et al (1995) using fluphenazine. Support for this hypothesis has also come from Hammock et al (1995) who studied the use of clozapine, and McDonough et al (2000) who studied the use of olanzapine, both antipsychotic drugs with a high affinity for D1 receptors, for SIB.

There has been only a limited effect of the antipsychotic drug chlorpromazine in this patient, even at high doses. The change to a new antipsychotic drug such as olanzapine or quetiapine may be considered.

There are withdrawal effects associated with antipsychotic drugs. Short-term withdrawal effects such as nausea and vomiting have been associated with antipsychotic drugs that have anticholinergic properties, such as thioridazine and chlorpromazine (Lacoursiere et al, 1976). Other long-term withdrawal effects such as worsening of tardive dyskinesia may also influence both the speed of withdrawal and the likelihood of success. Reduction of dose is more likely to be achievable than total withdrawal (Branford, 1996a, 1996b).

5. What alternative drug therapies may be of benefit?

A number of alternative drug strategies have been proposed for the treatment

of SIB. Those with the best evidence in the literature include the opiate antagonist naltrexone, and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine. Others such as propranolol, buspirone and clonidine are supported by case reports only.

The relatively large body of data on naltrexone contains contradictory reports of both success and failure to treat SIB. A series of controlled studies showed significant naltrexone-related reductions in SIB (Barrett et al, 1989; Bernstein et al, 1987; Herman et al, 1987; Sandman et al, 1990) which were dose related. Other studies have failed to find any such naltrexone-related effects (Szymansky et al, 1987; Zingarelli et al, 1992). A more recent study by Bodfish et al (1997) found that reduction of SIB was sustained in only two of nine subjects treated.

A recent retrospective review of the effect of divalproex (valproate semisodium) on aggression and self-injury showed that 88% of subjects had a reduction in maladaptive behaviour (Ruedrich et al, 1999).

Much of the support for SSRIs comes from studies of autism. SIB commonly presents in autism and the obsessive nature of the self-injury has led researchers to suggest that drug treatments used to treat obsessive compulsive disorder may be useful. The antidepressants used are predominantly those that affect serotonin reuptake and include clomipramine and the SSRI fluoxetine. Most reports involve either individual cases or small numbers (Primeau and Fontaine, 1987; McDougal et al, 1992; Markowitz, 1990; Lewis et al, 1995). Two large studies include those by Garber et al (1992), which involved 11 people, and Cook et al (1992), which involved 23 people with autistic disorder and 16 people with learning disabilities.

Garber et al (1992) found clomipramine to be effective in controlling a range of perseverative behaviours such as head-banging, head-slapping, hand-flapping and rocking in 10 out of 11 children, while McDougle et al (1992) achieved similar success with four out of five young adults with autistic disorder. Cook et al (1992) found fluoxetine at daily doses ranging from 20 mg to 80 mg led to significant improvement in 10 out of 16 individuals with learning disabilities and 15 of 23 individuals with autistic disorder. Other more recent studies

presented contradictory results about the benefits of SSRIs. These include: a retrospective review of seven patients (Fatemi et al, 1998) that showed some benefits but an increase in hyperactivity; a retrospective study of paroxetine that showed reduction of aggression but not SIB (Davanzo et al, 1998); a retrospective study of 37 adults with learning disabilities receiving either fluoxetine or paroxetine (Branford et al, 1998). Of the 37 patients, 15 showed no benefit and a further nine suffered a deterioration. The absence of total response indicates that no drug treatment is a 'magic bullet' in SIB.

Key points

- SIB, although not exclusive to people with learning disabilities, is particularly problematic in this population.
- There is no clear understanding of the aetiology of SIB.
- Clear documentation of baseline SIB is required, along with failure of psychological interventions, before initiating drug treatment. Attempts to monitor the efficacy and side-effects of medication should be made.
- The objective evidence to support the use of carbamazepine, lithium and naltrexone in SIB is poor.
- Antipsychotics, particularly those with affinity for D1 receptors, may be useful, but side-effects may be problematic.
- There is some evidence to support the efficacy of SSRIs in SIB, although their use remains controversial.

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29

Attention deficit hyperactivity disorder

Carol Paton

AB, a five-year-old child, was referred privately to a child psychiatrist by his GP. The family had recently returned from a three-year stay in America where AB had been prescribed methylphenidate. His parents explained to the GP that AB was 'a different boy' since he started taking medication one year ago. His attention span had improved, he was less impulsive and reckless, and not as 'out of control' as he had been. Several of AB's peers in America also took stimulants and the parents could not understand the GP's reluctance to prescribe. They were eager to obtain a further supply and requested an urgent private referral to a 'specialist'.

Questions

1. Why is there a difference in prescribing patterns for stimulants in the UK and USA?
2. What are the risks and benefits of stimulants in the treatment of attention deficit hyperactivity disorder (ADHD) and how should they be monitored? Are any other drugs helpful?
3. Should stimulants be given to children as young as five?
4. AB's father, a 32-year-old man, said that he too had been overactive as a child and still had trouble with his concentration and temper, which often got him into trouble, both at home and at work. He asked if his son's medication would help him. What advice would you give?

Answers

1. Why is there a difference in prescribing patterns for stimulants in the UK and USA?

European psychiatrists use the International Classification of Diseases diagnostic criteria (ICD10: World Health Organization, 1993) while American psychiatrists use those of the Diagnostic and Statistical Manual of Mental Disorders (DSMIV: American Psychiatric Association, 1994). Although both sets of criteria broadly recognize the triad of hyperactivity, poor ability to maintain attention and poor impulse control, ICD10 recognizes only hyperkinetic disorder (HD), which is considered to represent the severe end of the spectrum of ADHD as recognized by DSMIV (Anon, 1995; Swanson et al, 1998). HD affects one child in 200 in the UK, while the broader ADHD criteria applied in the USA has led to a 20-fold higher diagnosis rate (Drug and Therapeutics Bulletin, 1995). Diagnosis and treatment rates have increased dramatically in the USA over the last decade (Swanson et al, 1995), with recent reviews reporting the prevalence of ADHD to be between 3 and 11% of all children (Zametkin and Ermst, 1999). In line with increased diagnosis rates, the use of stimulants has risen eightfold in the last decade (Safer et al, 1996).

A recent report from the United Nations (1998) states that prescription rates for methylphenidate are rising annually by more than 100% in more than 50 countries. It advises governments 'to monitor prescription levels of methylphenidate in order to identify possible over diagnosis of ADHD and to prevent medically inappropriate use of the substance'. Concern over increases in the prescribing of stimulants in the UK led to the commissioning of the Regional Development and Evaluation Committee (DEC) report (Gilmore et al, 1998). This report strongly supports the use of methylphenidate in the short term and recommends more systematic research in the medium to long term (more than six months treatment).

It should be noted that most of the clinical research uses the broader ADHD criteria, response rates to stimulants are high (see question 2) and a substantial proportion of UK child psychiatrists support prescribing for children who do not meet the full ICD10 criteria for HD (Sayal and Taylor, 1997). The National Institute for Clinical Excellence (NICE, 2000) supports the use of stimulant medication in children as part of a comprehensive treatment plan for ADHD. Treatment should be initiated by a paediatrician or child psychiatrist and may be continued by a GP under shared-care arrangements. AB should, therefore, be referred to local specialist services in the first instance.

2. What are the risks and benefits of stimulants in the treatment of ADHD and how should they be monitored? Are any other drugs helpful?

Stimulants (methylphenidate and dexamphetamine) should only be used after specialist assessment and as part of a package of care that includes educational, psychological and behavioural assessment and intervention. They are effective in at least 70% of hyperactive children (Swanson et al, 1991). The exact mechanism of action of stimulants is unknown, although they are known to increase dopaminergic neurotransmission (methylphenidate by inhibiting monoamine uptake into the presynaptic neurone and dexamphetamine by increasing the release of monoamines into the synaptic cleft). Dysfunctional dopamine pathways in the frontal-basal ganglia are thought to be responsible for the clinical symptoms of ADHD, and the frontal lobes of affected children have been shown to be 10% smaller than

those of control children (Swanson et al, 1998). Stimulants are more effective in treating hyperactivity than inattention, although overactivity, attention span, impulsivity, aggression and social interaction should all improve with treatment. Social skills and general academic achievement may not improve (Zametkin and Ernst, 1999).

Evidence for the efficacy of methylphenidate beyond six months is generally considered to be poor, although one small trial has demonstrated that beneficial effects on hyperactivity, impulsivity, behavioural problems and attention persist for at least 15 months (Gillberg et al, 1997). The use of methylphenidate is strongly supported in the short term, with limited support for long-term use by DEC (Gilmore et al, 1998).

Methylphenidate is more widely prescribed than dexamphetamine as it is better tolerated. A third stimulant drug, pemoline, was withdrawn in 1997 because of reports of severe hepatic toxicity, at least six cases of which were fatal (CSM, 1997). Both available stimulants act within 30 minutes of administration and their effects last for up to four hours.

Methylphenidate is available as a sustained-release preparation, but this may be less effective (Fitzpatrick et al, 1992). The starting dose of methylphenidate is 5–10 mg daily and the dose should be titrated upwards against effect in weekly increments of 5–10 mg, up to a maximum dose of 60 mg daily (Ritalin SPC). Dexamphetamine is usually started at 2.5–10 mg daily, depending on the age of the child, and increased in weekly increments of 2.5 mg (Dexadrine SPC). The maximum daily dose required is usually 20 mg, although some children may need up to 40 mg. Treatment efficacy should be reviewed after one month and most prescribers consider withdrawing treatment at least once a year to evaluate continuing benefit (see also under side-effects below for further discussion of this point).

Stimulant drugs are associated with insomnia, decreased appetite, euphoria and, rarely, psychosis. These side-effects can be minimized by altering both the dose administered and its timing; they cause less than 4% of children to drop out of treatment (Rappley, 1997). The ADHD child has many behavioural problems and care must be taken to distinguish the effects of the 'illness' from side-effects of the

treatment. Placebo-controlled trials report very high rates of behavioural side-effects in placebo-treated children (Rappley, 1997). Tics can be unmasked or exacerbated but the risk is probably not as high as is commonly perceived, and they are not a contraindication to treatment. There is known to be an increased incidence of ADHD in children with Tourette's syndrome, complicating this issue (Cyr and Brown, 1998).

Despite early concerns about methylphenidate reducing the seizure threshold, its use in children with epilepsy appears to be associated with minimal risk (Gross-Tsur et al, 1997). Blood dyscrasias have been reported rarely, although monitoring of the full blood count (FBC) is not routine practice in all centres (Cosgrove, 1997).

The single side-effect of stimulant drugs that has engendered most concern is growth retardation. It is recommended that height and weight are measured at three monthly intervals and that if there is any evidence of growth retardation, a drug-free period should be considered. With careful use, final adult height is unaffected (Klein and Mannuzza, 1988; Rappley, 1997). It has been suggested that dexamphetamine may be more likely to cause growth retardation than methylphenidate (Cyr and Brown, 1998) but objective evidence to support this is poor.

Many other drugs have been used to treat ADHD, although all are considered to be second line to stimulants [reviewed by Cyr and Brown (1998)]. All are unlicensed. The majority of UK child psychiatrists would consider initiating one of these treatments if stimulants failed (Sayal and Taylor, 1997). This group of drugs is diverse and includes tricyclic antidepressants (TCA), bupropion (a noradrenergic antidepressant), monoamine oxidase inhibitors (MAOIs), carbamazepine, clonidine and various antipsychotic drugs.

While antipsychotics may ameliorate hyperactivity, they can have negative cognitive effects and the older drugs are associated with extrapyramidal side-effects (EPSEs). TCAs need to be given twice daily in children because of their relatively more rapid metabolism (Cyr and Brown, 1998). They are cardiotoxic and several cases of sudden death have been reported in children taking desipramine (Cyr and Brown, 1998). Selective serotonin reuptake

inhibitors (SSRIs) have been little studied, although some anecdotal reports of success exist. Clonidine may be used alone (in children with tics) or in combination with methylphenidate. Several cases of sudden death have been reported with the combination of clonidine and stimulants. Some children may require more than one drug [reviewed by Cyr and Brown (1998)].

An alternative theory of the aetiology of ADHD is that there is a deficiency of central nervous system fatty acids. Efalex, which is not a licensed medicine, is a source of essential fatty acids and can be bought over the counter from pharmacies. Some Health Authority prescribing committees allow its use on prescription for ADHD children. Most reports of efficacy are anecdotal.

Diets rich in artificial additives may worsen symptoms in some children (Carter et al, 1993), as may foods specific to individual children. Omitting the suspected food is always worthy of a trial as long as it does not lead to a nutritionally deficient diet. It may be difficult for children and adolescents to adhere to such diets.

3. Should stimulants be given to children as young as five?

It is generally believed that ADHD is difficult to diagnose in pre-school children as a wide variation in attention span and motor activity is considered to fall within the normal range. Some authors [reviewed by Zametkin and Ernst (1999)] claim that ADHD can be diagnosed in children as young as three, but this is controversial.

The product licence for methylphenidate (Ritalin SPC) clearly states that it should only be used in children aged over six years and should be discontinued during or after puberty. There are no clinical studies that demonstrate safety and efficacy in younger children. Indeed, some side-effects of methylphenidate, namely irritability and depressed mood, may occur more frequently in children under six (Rappley, 1997). In contrast, dexamphetamine is licensed for use in children as young as three (Dexadrine SPC) and is also licensed in adults for other indications.

It should be noted that drugs are frequently used 'off-label' in children and there has been recent concern about this practice in the general

medical literature (Turner et al, 1998). Almost 80% of UK child psychiatrists support the use of methylphenidate in children under six and 92% in children over 13 (Sayal and Taylor, 1997). Prescribing 'off-label' with the support of peers is recognized as good clinical practice by both the Medical Protection Society and the Medical Defence Union (Panting, 1999).

4. AB's father, a 32-year-old man, said that he too had been overactive as a child and still had trouble with his concentration and temper, which often got him into trouble, both at home and at work. He asked if his son's medication would help him. What advice would you give?

Support groups for adult ADHD sufferers have grown in the UK in recent years and there has been increasing interest in both the diagnosis and treatment of adult ADHD in the psychiatric literature. Adults whose diagnosis has been missed in childhood have been recognizing the symptoms of ADHD in themselves and requesting help. ADHD has a very strong genetic component (Goodman and Stephenson, 1989), so it is not surprising that many of these adults recognize their own problems when they become parents of an ADHD child who is successfully treated with stimulants. This would seem to be the case for AB's father. Relatives of ADHD sufferers are almost six times as likely to have ADHD themselves. The prevalence of depression, anxiety, alcohol and drug dependence, conduct disorder and antisocial personality disorder are also increased above population norms (Cosgrove, 1997).

Although ICD10 (World Health Organization, 1993) defines ADHD as a childhood diagnosis, it recognizes that symptoms can persist 'even into adult life', while DSMIV (American Psychiatric Association, 1994) criteria describe difficulties in 'school or work'. It is now recognized that approximately 25% of ADHD children will still have symptoms as adolescents, reducing to 10% at age 30 and virtually zero by age 40 (Toone and van der Linden, 1997; Swanson et al, 1998). Up to 3% of the adult population may have symptoms of ADHD (Wilens et al, 1995).

Follow-up studies of ADHD children have shown that hyperactivity decreases with age and that inattention and impulsivity (including a low frustration tolerance and explosive temper) predominate (Wilens et al,

1995). Delinquency in adolescence is predicted by ADHD at the age of eight (Farrington, 1993). Cyclothymia, impaired interpersonal relationships and being unable to organize, plan and anticipate consequences are common. One-third of ADHD children go on to receive a diagnosis of personality disorder as adults [with at least a 10-fold increase in the diagnosis of psychopathic personality disorder as compared to non-ADHD children: (Mannuzza et al, 1993)], and one-sixth go on to persistently abuse substances (Toone and van der Linden, 1997). Success in treating impulsiveness, temper and stress intolerance with stimulants in personality disordered adults has been reported (Wender et al, 1981).

When considering the case of AB's father, it should be noted that:

- Adult ADHD is not generally recognized by UK psychiatrists.
- The diagnosis can be difficult to make in the absence of a documented diagnosis in childhood, as many of the childhood criteria do not apply and diagnostic boundaries are blurred. The Wender Utah scale (Ward et al, 1993) is useful in this respect and requires that the patient's parents are interviewed. Detailed psychological assessment is essential.
- As in childhood ADHD, treatment is with stimulants which are potential drugs of abuse. Efficacy has been clearly demonstrated in clinical trials. One placebo-controlled crossover study (Spencer et al, 1995) demonstrated a 78% response rate to methylphenidate at a dose of 1 mg/kg daily in cases of adult ADHD where a retrospective diagnosis of childhood ADHD could be made (although no treatment was given at the time) compared to 4% with placebo. Similar findings exist for pemoline (Wender et al, 1981). The side-effect profiles in adults are similar to those in children. Methylphenidate is generally used in doses of 0.6–1.0 mg/kg daily and dexamphetamine up to 30 mg daily, both drugs given in two to three divided doses.
- Neither dexamphetamine nor methylphenidate are licensed for the treatment of ADHD in adults. There are no studies of the long-term efficacy of stimulants in adults.

As well as stimulants, adults with ADHD may respond to TCAs, bupropion, monoamine oxidative inhibitors (MAOIs), propranolol and possibly SSRIs. Noradrenergic and dopaminergic strategies seem to offer the most benefit (Wilens et al, 1995). Tomoxetine (Spencer et al, 1998) and bupropion (Wender and Reinherr, 1990), both selective noradrenaline reuptake inhibitors (SNRIs) have shown promise in adults. Desipramine is also effective (Wilens et al, 1996). Clonidine has not been studied in adults. Most evidence in this area is of poor quality and limited to small open studies and case reports.

It would seem reasonable, after further assessment, to offer AB's father treatment with a suitable antidepressant. If this fails he should be referred to a tertiary adult ADHD service for specialist assessment before stimulants are prescribed. The caveats above would dictate that this would be wise from a medico-legal standpoint.

Key points

- Stimulant drugs are very effective in the short-term treatment of ADHD.
- There is a lack of objective data supporting long-term use.
- Only a small proportion of children who could potentially benefit from treatment with stimulants currently receive them.
- Treatment should be initiated by a specialist. Ongoing assessment to monitor both efficacy and side-effects is essential.
- Methylphenidate is the drug of choice. It is licensed for use in children aged six to puberty. In some cases it is appropriate to treat children outside this age range.
- Symptoms of ADHD can persist into adult life. Treatment is controversial.

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Childhood depression

Stuart Banham

30

BR, a 12-year-old Caucasian girl, was referred to the child and adolescent psychiatric services by her GP. Her mother had become increasingly anxious over BR's poor school attendance because of multiple somatic symptoms: abdominal pains, headaches and chest tightness.

The GP had been unsuccessful in elucidating a cause for these symptoms and so referred BR to the local child psychiatric services for assessment of possible school refusal and anxiety disorder.

When interviewed by the child psychiatrist, it became apparent that there had been a gradual deterioration in BR's academic performance over the preceding 12 months, linked with a lack of interest in friends and other activities. There was also a considerable level of marital disharmony at home, which BR blamed on herself. There was a positive family history of psychiatric illness; both

BR's mother and grandmother had been treated for adult depression in the past.

Originally, the GP had been reluctant to prescribe any medication but after BR's symptoms started to deteriorate he had prescribed amitriptyline 50 mg daily 'to help ease her anxiety'. This was switched to fluoxetine 10 mg daily by the child psychiatrist.

Questions

1. Comment on the initial choice of antidepressant used by the GP.
2. Was the switch to fluoxetine appropriate?
3. What further treatment options are available for BR?
4. What is the prognosis in childhood-onset depression?

Answers

1. Comment on the choice of antidepressant used by the GP.

Tricyclic antidepressants (TCAs) have been widely used to treat depression in children and adolescents. The rationale for their use stems largely from the observation that childhood depression appears to be a continuous syndrome with adult depression and so it would be reasonable to expect that children would respond to antidepressant therapies in a similar way to adults (Geller, 1994). However, children respond to antidepressants, particularly TCAs, in a different manner to adults.

Several TCAs, including imipramine, desipramine, nortriptyline and amitriptyline, have been studied in double-blind placebo-controlled trials of childhood or adolescent depression (Geller et al, 1999). These studies failed to show a statistically significant difference between active agent and placebo. Many studies employed small sample sizes and so possibly lacked the statistical power to detect any difference (type II error). Attempts by Hazell et al (1995) to overcome this problem, by conducting a meta-analysis of TCAs in treating child and adolescent depression, again found no statistically significant difference between placebo and treatment arms.

Despite pooling 12 trials into two groups, depending on how results were reported, the sample sizes in each group remained quite small, (78 and 97) respectively. It is thus possible that lack of sufficient statistical power may have remained the reason for a failure to detect any difference.

Apart from small sample sizes, other limitations in trial design may explain the lack of observed effect: trials including patients with mild or moderate depression (which is known in adults to respond poorly to antidepressants), inadequate trial length, or too low doses being used (Birmaher, 1998). It is also possible that biological or developmental factors may be of importance. For example, compared with the serotonergic nervous system, the noradrenergic system matures much later (Birmaher et al, 1998) and may not be fully functional in adolescents. Also, it might be that, in common with other disease states such as diabetes mellitus, early-onset depression represents a more severe form of the illness and so is more likely to be treatment resistant (Geller et al, 1996).

Safety is an important consideration in the drug treatment of childhood depression. Since 1990 there have been seven cases of sudden death reported in children prescribed TCAs - six with desipramine and one with imipramine (Varley and McClellan, 1997). In the majority of cases ECG monitoring was performed, doses used were within acceptable limits (<5 mg/kg) and in only two cases was there a family history of cardiac disease. Post-mortem examinations did detect some cardiac pathology in two of the children that was not apparent before death. Studies of TCAs in children have identified potentially toxic ECG changes. These include first-degree atrioventricular (AV) block (detected in three out of seven children treated with imipramine 5 mg/kg), increases in mean heart rate, and statistically significant increases in P-R and QRS interval (Riddle et al, 1993). Thus, in children, as in adults, TCAs have an important effect on cardiac impulse conduction. However, in most of these studies detected ECG changes may have been statistically significant but not all authors agree on their clinical significance (Riddle et al, 1993). Overall, it is questionable whether, in the absence of robust efficacy data, it is right to expose children to the potential cardiac risks of TCA therapy.

2. Was the switch to fluoxetine appropriate?

The evidence supporting a therapeutic effect for selective serotonin reuptake inhibitors (SSRIs) in childhood depression is marginally better than for TCAs. In a double-blind randomized trial, Emslie et al (1997) found a statistically significant difference in the response rate for fluoxetine over placebo. This study randomized 96 children, seven to 17 years old, with non-psychotic major depressive disorder to receive fluoxetine 20 mg daily or placebo for eight weeks. Using the Clinical Global Impression (CGI) scale to define response, 27 out of 48 children who received fluoxetine and 16 out of 48 who received placebo were judged to have responded. However, only 15 out of 48 who received fluoxetine were described as in complete remission at the end of the study.

Another study, by Simeon et al (1990) included 40 adolescents, 13–18 years old, with major depressive disorder. Approximately two-thirds of children from both groups showed a response, and the difference between placebo and fluoxetine was not statistically significant. Emslie et al (1997) attributed the positive findings of their study to their relatively large sample size, the exclusion of patients with psychotic depression, bipolar disorder and a family history of bipolar illness, and the recruitment of patients from a range of socio-economic backgrounds. Others have commented that the positive result may have been a consequence of the subjects in the study having a later onset and less severe depression than many of the subjects in previous TCA studies (Geller et al, 1996).

There is some evidence to support the efficacy of other SSRIs in treating child or adolescent depression. Ryan and Varma (1998) described a large study of adolescent depression that compared paroxetine, imipramine and placebo and reported that the results of this study were extremely positive, with paroxetine being superior to both placebo and imipramine. This study has not yet been published in full in a peer-reviewed journal. A published, open trial of paroxetine in childhood depression has also demonstrated efficacy (Rey-Sanchez and Gutierrez-Casares, 1997). Forty-five children, under 14 years old, with a DSM III-R diagnosis of major depressive disorder, were given paroxetine initially at 10 mg daily and then titrated according to

clinical response. All patients experienced a complete remission of symptoms within the eight-month study period. Response was measured using the CGI scale, a relatively crude measure. Paroxetine in this study was well tolerated, with only four children experiencing mild gastrointestinal side-effects, with no withdrawals as a consequence.

Alderman et al (1998) reported on the safety and efficacy of sertraline in the treatment of depression or obsessive-compulsive disorder. This open study in children of six to 13 years old demonstrated that doses of up to 200 mg daily were well tolerated and depressive symptoms improved as measured using the CGI.

Although efficacy would seem to be better demonstrated with SSRIs than TCAs it still remains far from satisfactory. To date only one randomized controlled trial, with one SSRI, has demonstrated a statistically significant effect against placebo. Although evidence from open-label studies is encouraging it should be remembered that such studies are less robust than double-blind placebo-controlled studies. Open-label studies with TCAs have also demonstrated efficacy that has not been replicated in blinded studies and in all studies of childhood depression there has been an unusually high placebo response rate. Given the safety concerns surrounding TCA therapy it would be prudent to use an SSRI as first-line pharmacotherapy in childhood depression. Non-drug interventions such as cognitive therapy, cognitive behavioural therapy or interpersonal therapy might be more appropriately tried before any pharmacological intervention (Geller et al, 1999; Hughes et al, 1999). Further discussion of these interventions is outside the scope of this book.

3. What further treatment options are available for BR?

Evidence supporting the use of other antidepressants in childhood or adolescent depression is extremely scant. A placebo-controlled study examining the efficacy of venlafaxine in children of eight to 17 years old failed to demonstrate any significant effect (Mandoki et al, 1997). Again, both the placebo and active treatment group showed substantial improvements in the six-week study but a significant number (45%) of the venlafaxine-treated group suffered from nausea and weight gain. The authors

attributed the lack of efficacy to the low doses of venlafaxine used (37.5 mg daily in children eight to 12 years old and 75 mg daily in adolescents 13–17 years old) and the relatively short trial duration. In all probability, with a sample size of only 40 patients, this study did not have the necessary statistical power to demonstrate an effect even if there was one.

Nefazadone has been studied in children and adolescents from seven to 17 years old (McConville et al, 1998). Although the primary purpose of this open study was to examine the pharmacokinetics of nefazodone in this age range, it was found that doses up to 300 mg daily in children under 12 years old and 600 mg daily in those 12–17 years old were well tolerated, and appeared to provide some improvement in depressive symptoms.

Based on the observation that a high proportion of children with treatment-resistant depression will later develop a bipolar illness, Geller et al (1996) proposed the consideration of lithium therapy. In their small-scale study amongst children with either loaded or multigenerational family histories of depression, they failed to demonstrate a significant difference between treatment and placebo groups.

Ryan et al (1988) demonstrated some benefit from administering the monoamine oxidase inhibitors (MAOIs), phenelzine and tranylcypromine, to children who had failed to show an adequate response to TCAs. It may now not be supportable to prescribe MAOIs in a group of poor responders as other, safer, alternatives have been marketed since this study was completed.

Although rarely used, electroconvulsive therapy (ECT) has been shown to be of benefit in some adolescents who failed to respond adequately to pharmacological interventions (Strober et al, 1998). In this small study, ECT was administered to 10 patients with psychotic depression: nine of the 10 patients showed dramatic improvements as judged by Hamilton Depression Rating Scale (HAMD scores). A separate study has shown that adolescent recipients of ECT have fairly positive attitudes to treatment as they found it less aversive than the illness for which it was given (Walter et al, 1999).

4. What is the prognosis in childhood-onset depression?

Sixty per cent of children diagnosed with depression recover within one year, although interpersonal difficulties can persist: 80% of these children will have a further episode within five years (Mirza and Michael, 1996). One-third of children who experience an episode of major depression before the age of 11 develop bipolar illness later in life (Geller et al, 1996). This compares with a risk of 20% when depression occurs for the first time in adolescence and 5–18% when the index episode is after the age of 18.

Key points

- No randomized controlled trial has demonstrated any TCA to be effective in the treatment of childhood depression.
- TCAs, particularly imipramine and desipramine, are particularly cardiotoxic in children.
- There is one randomized controlled trial that demonstrates the efficacy of fluoxetine in childhood depression: SSRIs, in general, seem to be well tolerated.
- There is no evidence to support the efficacy of venlafaxine; it is also poorly tolerated.
- No antidepressant is licensed for use in children or adolescents.
- In comparison with adult-onset depression, childhood depression has a poor prognosis, with up to 40% of children later developing a bipolar illness.

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31

Alcohol detoxification and the maintenance of abstinence

Carol Paton

MB, a 41-year-old divorced publican, was admitted to hospital for alcohol detoxification. He was a known lifelong heavy drinker and the current admission was his third for detoxification in the last two years. MB had also undergone two community detoxifications in the previous five years. Past detoxifications had been uncomplicated, with the exception of one grand mal seizure two days into his most recent admission.

For the past three months MB had been drinking a bottle of spirits and several cans of strong lager each day, often beginning as soon as he got up in the morning. He smoked 20 cigarettes per day but did not abuse any other substances. MB regularly purchased cimetidine from a pharmacy for symptoms of reflux oesophagitis. There was no other medical or psychiatric history of note.

On admission, MB had a marked tremor, was sweating and nauseous, and his pulse and blood

pressure were moderately raised. Physical examination was otherwise unremarkable.

Laboratory tests were as follows:

Gamma glutamyl transferase (GGT) (reference range 10–55)	*840 U/l*
Alkaline phosphatase (ALP) (reference range 25–115)	*150 U/l*
Alanine aminotransferase (ALT) (reference range 5–30)	*40 U/l*
Aspartate aminotransferase (AST) (reference range 7–40)	*73 U/l*
Mean corpuscular haemoglobin (MCV) (reference range 78–98)	*106 fl*

Glucose, albumin, bilirubin and clotting were normal.

The diagnosis of an alcohol dependency state was made and MB was prescribed:

chlordiazepoxide:	*25 mg four times a day, reducing to zero over seven days*
thiamine:	*300 mg orally in the morning*
phenytoin:	*100 mg TDS for four days* *50 mg TDS for two days* *50 mg BD for two days then stop.*

Questions

1. What are the symptoms of alcohol withdrawal and how should they be managed?
2. What is the role of phenytoin in the management of withdrawal seizures?
3. Is the dose of thiamine prescribed for MB adequate?
4. What pharmacological strategies are available to prevent relapse into problem drinking and how effective are they?

Answers

1. What are the symptoms of alcohol withdrawal and how should they be managed?

Chronic ethanol consumption desensitizes the GABA-benzodiazepine receptor complex, α_2-adrenergic receptors and possibly also glutamate receptors (Verbanck, 1995). Sudden

re-sensitization of these receptors during detoxification leads to the clinical syndrome of alcohol withdrawal, characterized by tremor, irritability, insomnia, anxiety, agitation and sensory hyperactivity. Delirium tremens, characterized by visual and auditory hallucinations, disorientation, tremulousness and paranoid ideation constitute a more severe withdrawal state. Seizures (see question 2) and Wernickes encephalopathy (see question 3) can also occur. Although subjective and physiological disturbances are most intense in the first week, anxiety, irritability, sleep disturbance and emotional lability can persist for months in heavily dependent individuals (Shaw, 1995; Verbanck, 1995), and are a frequent cause of relapse into problem drinking.

Management of alcohol withdrawal involves the treatment of symptoms, as well as the recognition and treatment of the likely complications. Rating scales such as the Clinical Institute Withdrawal Assessment-Alcohol (CIWA-Ar: Sullivan et al, 1989) are useful for monitoring symptoms and high scores have been shown to reliably predict seizures and delirium tremens (Mayo-Smith, 1997).

MB has a history of multiple detoxifications, has been consuming very large quantities of alcohol and has had a withdrawal seizure in the past. These factors all predict a complicated withdrawal on this occasion (Shaw, 1995). Outpatient detoxification would clearly not be an appropriate option for MB.

Drugs that exhibit cross-tolerance with alcohol are effective in the control of withdrawal symptoms. Benzodiazepines and chlormethiazole are the most widely used agents in the UK. Barbiturates are frequently used in the USA (Mayo-Smith, 1997). Chlormethiazole mediates its effects through the picrotoxin/barbiturate site on the GABA receptor complex (Morgan, 1995) and also has glycine potentiating activity (Ogren, 1986). Benzodiazepines act through the GABA-benzodiazepine receptor complex.

Diazepam is more likely to be abused than chlordiazepoxide (Mayo-Smith, 1997) and is thought to be less safe than diazepam if taken in combination with alcohol (Shaw, 1995). Longer acting benzodiazepines, such as chlordiazepoxide, give a smoother withdrawal but may accumulate, particularly in those with hepatic

impairment. Oversedation, confusion and ataxia may result. Respiratory depression can be reversed by flumazenil but care must be taken not to induce seizures. Shorter acting drugs such as oxazepam are safer in hepatic impairment.

Chlormethiazole is structurally related to thiamine. It can cause transient nasal congestion and irritability, as well as increased bronchial secretions. Unlike most other anticonvulsants, chlormethiazole does not induce hepatic enzymes and actually inhibits the hepatic enzyme, inducing the effects of alcohol. It has been postulated that this action may lead to a hepatoprotective effect against toxic oxidation products in the livers of alcoholics (Majumdar, 1991).

Although the bioavailability of chlormethiazole is less predictable than that of chlordiazepoxide (ABPI), its half-life is considerably shorter (4 versus 15 hours) making titration against symptoms easier and accumulation less likely. Regimes where medication dose is titrated against symptoms have been found to lead to the administration of significantly less medication over shorter time frames while offering equivalent symptom control to fixed-dose reducing regimes (Mayo-Smith, 1997). Three comparative trials of chlordiazepoxide and chlormethiazole have been published and no difference in efficacy has been demonstrated (Duncan and Taylor, 1996).

Consumption of chlormethiazole in combination with alcohol is thought to be responsible for around 30 deaths per year, leading to recommendations that it should not be used for more than nine days (ABPI), should be restricted to specialist units and should only be used in outpatients under exceptional circumstances (CSM, 1987). It has, however, been pointed out that benzodiazepines are also an important cause of morbidity and mortality and that the differential effect for chlormethiazole may have been exaggerated (Shaw, 1987). Chlormethiazole is a safe drug when used correctly (Morgan, 1995) and 14% of specialist inpatient detoxification units still use chlormethiazole first line (Agarwal et al, 1997).

Clonidine, carbamazepine and antipsychotics are sometimes used as adjuncts during detoxification. All are inferior to benzodiazepines when used alone and none have been shown to

reduce the incidence of delirium tremens (Mayo-Smith, 1997).

MB has no evidence of hepatic impairment and the chlordiazepoxide regime prescribed for him is appropriate, although it is possible that he may require a higher initial dose due to his very high alcohol consumption. A symptom rating scale such as the CIWA-Ar should ideally be used to determine his dosage requirements. A more flexible regime may lead to decreased overall consumption.

2. What is the role of phenytoin in the management of withdrawal seizures?

Seizures are most common in the first 48 hours of detoxification (Morgan, 1995) and never occur later than 72 hours when the withdrawal is from alcohol alone (Robertson and Sellers, 1978). MB has been prescribed chlordiazepoxide for the control of general withdrawal symptoms. Chlordiazepoxide has anticonvulsant properties and adequate doses have been shown to eliminate withdrawal seizures completely, even in those who have a documented history during previous detoxifications (Lechtenberg and Worner, 1990). In one frequently quoted trial of 157 patients admitted to hospital for alcohol detoxification and randomly allocated to receive phenytoin or placebo in addition to the standard chlordiazepoxide regimen (Sampliner and Iber, 1974), 11 out of 79 patients allocated to placebo and two out of 70 patients allocated to active treatment experienced at least one recorded seizure. Serum levels of phenytoin were monitored in 18 patients (none of whom were included in the trial!) and a mean level of 3 μg/l was found after the first day of treatment. The authors concluded that although serum phenytoin levels were low, a therapeutic effect was demonstrated, and they recommended prophylactic phenytoin for patients undergoing alcohol withdrawal who have a history of seizures. This influential trial has many methodological weaknesses. For example, the chlordiazepoxide consumption was not recorded for each patient group and other large studies (eg Rothstein, 1973) have shown that adequate doses of chlordiazepoxide alone result in excellent seizure prophylaxis. Other studies (eg Alldredge et al, 1989) have shown that even when administered intravenously in doses capable of producing therapeutic serum levels, patients randomized to receive

phenytoin did not have a lower incidence of seizures than those in the placebo group. This is not surprising as the mechanism of alcohol withdrawal seizures is poorly understood and may not be amenable to alteration by phenytoin.

Phenytoin is a toxic drug and can be complex to use. In order to achieve a therapeutic level (10–20 mg/l) a loading dose of 500–1000 mg would have to be given to a 70 kg man. The use of a fixed dose regime is unlikely to give therapeutic serum levels when they are needed most (in the first 48 hours) and may accumulate to give toxic levels by the end of the treatment period in the presence of hepatic dysfunction. This is because metabolism changes from following first-order to zero-order kinetics within the therapeutic plasma level range. A small increase in dose can lead to a disproportionate rise in serum levels. Toxic concentrations of phenytoin can readily develop in patients given drugs that inhibit hepatic enzymes or displace phenytoin from binding sites on albumin, and in patients who have impaired hepatic function (due to the effects of decreased plasma albumin concentrations, decreased ability of the liver to metabolize and possibly decreased affinity of phenytoin for albumin in the presence of severe jaundice).

Side-effects of phenytoin include nausea and vomiting, cardiac arrhythmias and central nervous system (CNS) disturbances, such as slurred speech, nystagmus and confusion. These effects increase in frequency and severity as the plasma level rises above 20 mg/l. Phenytoin should not be withdrawn suddenly as withdrawal seizures may be precipitated. The complex pharmacokinetics of phenytoin demand a thorough evaluation of both concomitant disease states and drug therapy in order to ensure safe and efficacious use of the drug.

The use of phenytoin as an adjunct in alcohol detoxification cannot be justified as:

- Without a loading dose, the levels reached are highly unlikely to be in the therapeutic range when they are needed most.
- Hepatic impairment is possible, leading to a high risk of phenytoin toxicity.
- Phenytoin is a toxic drug which is involved in many drug interactions.

- An adequate chlordiazepoxide regime will protect against seizures.

In addition, MB has been taking cimetidine. Cimetidine inhibits the metabolism of phenytoin, making serum levels even more difficult to predict.

When systematically evaluated, only sedative hypnotic drugs, i.e. those that show cross-tolerance to alcohol, have ever been shown to be effective in the treatment of alcohol withdrawal seizures.

3. Is the dose of thiamine prescribed for MB adequate?

Thiamine has poor oral bioavailability and is absorbed via a saturable mechanism. A normal healthy adult can, it is thought, absorb no more than 4 mg per day, no matter what dose is administered orally. This amount is reduced substantially in those who are chemically dependent on alcohol. Figures of 0.5 mg per day have been quoted for chronic alcoholics who cease consumption of alcohol and 0.05 mg per day for those who continue to drink (Cook and Thompson, 1997). The body requires 1 mg of thiamine per day and can store up to 30 mg (McCormick, 1988).

Malabsorption, poor diet, reduced storage and utilization, and increased requirement all contribute towards thiamine deficiency in alcoholics (Reuler et al, 1985).

Thiamine crosses the blood-brain barrier by both active transport and passive diffusion. Active transport mechanisms are saturated at levels barely above normal CNS requirements so, in order to treat deficiency rapidly, large doses must be available to diffuse passively into the brain (Cook and Thompson, 1997). A number of studies have shown that oral thiamine does not improve CNS or peripheral vitamin status (eg Thompson et al, 1983).

Thiamine plays an essential role as a coenzyme in the regulation of glucose utilization by the brain. Alcoholics use ethanol as their energy source and when this is removed abruptly (as it is during detoxification) they again need to rely on glucose, which they cannot utilize due to thiamine deficiency: Wernickes encephalopathy may result. Wernickes encephalopathy classically presents with clouding of consciousness, ophthalmoplegia and ataxia, although only 10% of patients present with this 'classical' picture (Cook and Thompson, 1997) and as

few as 20% of post-mortem proven cases are diagnosed in life (Reuler et al, 1985). The mortality rate is up to 20% (Reuler et al, 1985).

Vulnerability to developing Wernickes encephalopathy may be genetically determined (Combs, 1992). Delirium tremens further increase the demand for thiamine, the risk of Wernickes encephalopathy and subsequent progression to Korsakoffs psychosis (Victor et al, 1989). Large carbohydrate loads in malnourished thiamine-deficient patients can also precipitate Wernickes encephalopathy (Reuler et al, 1985).

Although it has been known for many years that thiamine can reverse the symptoms of Wernickes encephalopathy and prevent permanent neurological sequela, this has never been studied systematically (Cook and Thompson, 1997). The resulting lack of clarity over the appropriate dose of thiamine has led to different units adopting widely different policies. The use of oral thiamine is still common in the UK (Agarwal et al, 1997).

Parenteral thiamine is associated with a risk of anaphylaxis, although this has never been quantified. Spontaneous reports to the Committee on Safety of Medicines (CSM) were of the order of four reports for every one million doses of intravenous (IV) Parentovite and one report for every five million doses of intramuscular (IM) Parentovite sold. This is likely to be a huge underestimate as anaphylaxis is a well-recognized side-effect of parenteral thiamine and spontaneous reporting rates are likely to be low. The risk of anaphylaxis is higher with IV thiamine (where it is strongly associated with the rate of administration) than IM administration (CSM, 1989). The IM injection is likely to be painful (total volume 7 ml).

Parentovite was withdrawn in 1991 due to manufacturing problems and has since been replaced with Pabrinex, an almost identical preparation. Each pair of Pabrinex IVHP or IMHP ampoules contain thiamine 250 mg, riboflavine 4 mg, pyridoxine 50 mg, nicotinamide 160 mg and ascorbic acid 500 mg (Pabrinex SPC).

The oral thiamine regime prescribed for MB is inadequate. He should receive Pabrinex IM high potency (IMHP) or IV high potency (IVHP), one pair daily for five days. The IMHP ampoules must be mixed together

before administration, but may be given in two or more injection sites. The IVHP preparation should ideally be administered in 100 ml of saline. It should be noted that the dose of Pabrinex required for the prophylaxis and treatment of Wernickes encephalopathy differ. One pair of ampoules daily is probably adequate for prophylaxis while up to two pairs three times a day may be required for treatment of neurological symptoms (Cook and Thompson, 1997). In established Wernickes encephalopathy, treatment should be continued for as long as improvement is seen. The CSM (1989) has given very clear guidelines that facilities for treating anaphylaxis should be available whenever parenteral thiamine is administered. This should be ensured.

4. What pharmacological strategies are available to prevent relapse into problem drinking and how effective are they?

MB's previous history of failed detoxification, the extent of his current drinking, his physical complications and his probable relationship problems, make total abstinence the only option for him. He should be encouraged to give serious thought to changing his occupation. After detoxification is complete, MB should be assessed for the presence of co-morbid depression or anxiety. If present, treatment of these conditions will improve prognosis.

Continued drinking is influenced by both positive reinforcement (the reward of a high) and negative reinforcement (the need to avoid withdrawal). If MB can be helped to understand why he drinks, then his chances of gaining control will increase. In the medium to long term MB should receive ongoing psychological support and adjunctive medication to prevent relapse into problem drinking. It should be noted that the majority of trials that examine the efficacy of adjunctive medication originate from tertiary centres. Many exclude patients with physical illness, multiple previous detoxifications and unstable domestic circumstances. Some randomize as few as 30% of screened patients. All patients receive supportive psychotherapy (likely to differ between centres and unlikely to be available to all patients in the 'real' world).

There is no accepted endpoint or definition of relapse in alcohol-dependent patients. Trials variably report total abstinence, duration of initial abstinence, total number of

drinking days, quantity of alcohol consumed, biological markers such as GGT or MCV and assessment of craving. In the longer term, the placebo response, attrition rate and relapse rate are high and compliance is poor. Inter-individual responses to different drugs vary markedly. There are no randomized controlled trials that compare active drugs.

Acamprosate (a GABA analogue and glutamate antagonist which also increases serotonin in the CNS and antagonizes noradrenaline (Schaffer and Naranjo, 1998)) and disulfiram (an irreversible inhibitor of hepatic aldehyde reductase) are licensed in the UK for the maintenance of abstinence. Naltrexone is licensed in the USA. The evidence for each of these interventions is summarized below.

Acamprosate: Treatment groups show higher rates of continuous abstinence and abstinent days, but the effect sizes are not large. For example, in one trial that randomized 224 patients to receive acamprosate and 224 placebo (Whitworth et al, 1996), 41 of the acamprosate patients and 16 of the placebo patients were continuously abstinent at the one year endpoint. It can be calculated that nine patients need to be treated for one year for one patient to remain abstinent (i.e. number needed to treat = 9).

Although the dose for acamprosate is based on body weight, trials show a trend for six tablets per day being the most effective dose, irrespective of weight. Treatment should be started during, or as soon as possible after, detoxification and continue for one year. Efficacy beyond this point is unknown. The main side-effect is diarrhoea. Acamprosate combined with disulfiram may offer added benefit (Wilde and Wagstaff, 1997).

Naltrexone: Alcohol consumption leads to an increase in endogenous opioid activity (Schaffer and Naranjo, 1998) and this may be genetically determined. Naltrexone, a pure opioid antagonist, is thought to block the high experienced after alcohol consumption. Clinical studies have shown that it can be effective in reducing intake, although it does not always result in total abstinence (Schaffer and Naranjo, 1998). Success is higher in those with greater somatic distress and greater craving.

A starting dose of 25 mg increased to

50 mg after a few days should be used. Nausea, vomiting, anxiety, headache and fatigue can occur when treatment is initiated, and are thought to constitute a mild opiate withdrawal reaction. Early studies showed increases in liver transaminases with very high doses of naltrexone, and although it has not been shown to be hepatotoxic at the normal therapeutic dose of 50 mg daily, it is usually avoided where there is existing hepatic impairment. Naltrexone stimulates the release of luteinizing hormone which may lead to unexpected pregnancy. The successful use of PRN naltrexone (where a dose is only taken prior to entering a high-risk situation) has been described (Schaffer and Naranjo, 1998).

Disulfiram: Blocks the metabolism of alcohol and leads to an increase in serum acetaldehyde levels, resulting in the unpleasant symptoms of facial flushing, nausea and weakness. It is involved in many drug interactions. Although disulfiram has been shown to be effective in open studies, when tested under the more rigorous conditions of a double-blind placebo-controlled trial, disulfiram and placebo have been shown to be equally effective, leading to the conclusion that it is the fear of a disulfiram reaction that prevents drinking (Verbanck, 1995). Fear may select more motivated individuals. Many studies have been conducted in carefully selected groups, often with a coercive element (Hughes and Cook, 1997). Total abstinence rather than reduced consumption has been the aim of disulfiram studies. The ability of disulfiram to reduce consumption has been poorly evaluated. As with naltrexone, the successful use of disulfiram on a PRN basis has been described (Verbanck, 1995). Calcium carbimide, which has a similar mode of action to disulfiram, is available on a named-patient basis.

Other approaches: Reward is associated with dopamine release and it is theoretically possible but it is not proven that antipsychotics (via blockade of post-synaptic dopamine receptors) may prevent relapse in some. Bromocriptine has been shown to reduce craving in those with the A1 allele of the D2 receptor (Wilde and Wagstaff, 1997).

Selective serotonin uptake inhibitors (SSRIs) are of limited benefit, although in some studies they have produced small decreases in consumption, and men have fared better than women (Verbanck, 1995). Whether this

represents any more than treatment of an undiagnosed depressive illness is unknown. Buspirone may have a place in some patients where anxiety is prominent. Many other drugs, including ritanserin, viloxazine, ondansetron, desipramine and tiapride, have been studied (Verbanck, 1995). Trials have generally been small and results need replicating.

licensed for the 'maintenance of abstinence' after detoxification. Naltrexone is also used for this purpose.

- The majority of trials originate from tertiary centres and exclude a large proportion of patients commonly seen in practice: the generalizations of their findings is questionable.

Key points

- Management of alcohol withdrawal involves the treatment of symptoms as well as the recognition and treatment of the likely complications.
- Chlordiazepoxide is the most widely used treatment for alcohol withdrawal. Other drugs that exhibit cross-sensitivity with alcohol are also effective.
- The use of phenytoin as an adjunct to protect against seizures during detoxification is not supported by an evidence base.
- Thiamine has poor oral bioavailability. If thiamine deficiency is suspected, parenteral administration is essential.
- Disulfiram and acamprosate are

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32

Methadone initiation

Lucy Reeves and Janie Sheridan

AC is a 25-year-old, single, unemployed, Caucasian male, who lives on his own in a one-bedroomed flat. He presented to drug treatment services claiming to be addicted to heroin and requesting a methadone prescription.

AC claims to use 0.5–1 g of illicit heroin daily, for which he pays £30–60 at the current 'street' price. He injects the drug intravenously, typically three times a day, and has been using at this level for one year. He will occasionally buy 60 ml of illicit methadone if he cannot buy heroin; this amount seems to prevent withdrawal symptoms. He also uses around 50–60 mg daily of illicitly obtained diazepam, smokes 1/8 oz of cannabis over a week and drinks four to five cans of strong (9%) lager daily. He does not use amphetamines or cocaine/crack cocaine.

AC started smoking heroin at the age of 18 and began to use it daily at about the age of 20. He

was previously prescribed 30 mg methadone daily by his GP for a period of six months but this ended one year ago. He has not been engaged with any other drug or alcohol services and has had no other treatment or periods of abstinence, except while being in prison for one month.

Treatment plan:

Initially, a full assessment of the patient's drug use, confirmation of dependence and assessment of level of dependence. Assuming dependence to opiates is confirmed, induction onto methadone, stabilization of dose and setting up of future treatment plan to deal with his associated use of other drugs and alcohol, and his health, psychological and social needs.

Questions

1. What are the aims of assessment?
2. What are the main factors to be aware of during the methadone initiation and stabilization period?
3. What significant drug interactions need to be considered?
4. What plans should be implemented for continuing treatment?

Answers

1. What are the aims of assessment?

The aims of assessment are:

1. The confirmation of opiate dependence and evaluation of the extent and nature/severity of the patient's drug-related problems, including those other than opiates. The assessment should cover medical, psychological and social aspects, and give special attention to mental health issues, co-morbidity, suicide risk and other risk behaviours (such as injecting, involvement in the sex industry and criminal activities)
2. To establish what the patient wants from treatment (what are their

expectations, concerns, restrictions) and what is their level of motivation to change
3. To formulate a treatment plan, incorporating medical, psychological and social interventions

A diagnosis of substance dependence/misuse may only be made following a full assessment. This assessment must include a full drug and alcohol history of past and current use, including previous contacts and treatments with drug services. It is essential to find out what drugs, including alcohol, the patient uses, in what quantity and the frequency of use, route of administration, and duration of use at this level. Confirmation of dependence should be based on the patient's self-reported history of drug use, in conjunction with objective signs such as evidence of recent injecting, several positive urine analyses for opiates and/or metabolites, and visible signs of withdrawal, e.g. sweating, 'goose flesh', vomiting, dilated pupils, tachycardia, hypertension and agitation.

It is useful to know which treatments have been tried before and whether or not they were successful, as well as any significant periods of abstinence, how this was achieved and the reasons for relapse. The assessment should also cover medical, psychiatric, forensic and social history to identify any significant issues.

It is also important to discover why the patient has presented for treatment, what their level of motivation to make changes in their drug using behaviour is, and what their goals and expectations from treatment services are. No treatment will be successful if the patient finds the offered treatment intervention unacceptable or is unwilling to cooperate. Treatment aims should be set at an appropriate level to meet the patient's needs.

This is also an opportune time to make interventions regarding harm reduction. Information, for example, on needle exchange services, hepatitis and HIV testing, hepatitis A/B vaccinations, overdose risks and general healthcare issues, can be given to the patient during the course of assessment as relevant. The assessment is also an important point of contact to encourage engagement with services and enhance motivation for changes in their drug-using lifestyle. The treatment plan should incorporate medical,

psychological and social interventions to address the multifaceted problem of substance misuse.

Decision to prescribe an opiate substitute

Prescribing of an opiate substitute should only be initiated as part of a clear treatment plan with mutually agreed goals between prescriber and patient. Goals should be realistic and flexible. Department of Health Guidelines (1999) recommend that:

'a prescription for substitute medication should only be considered if:

- *the drug/s is/are being taken on a regular basis, particularly for daily misuse;*
- *there is convincing evidence of current dependence (including objective signs of withdrawal symptoms wherever possible);*
- *the patient is motivated to change at least some aspect of their drug use;*
- *the assessment (history, urine toxicology, drug diary) clearly substantiates the need for treatment;*
- *the doctor is satisfied that the patient will co-operate and demonstrate adequate compliance with the prescribing regime.'*

The treatment aims of prescribing substitute medication are:

- To reduce or prevent withdrawal symptoms.
- To stabilize (and reduce) drug intake.
- To stabilize lifestyle.
- To reduce drug-related harm (particularly injecting behaviour).
- To help maintain contact and provide an opportunity to work with the patient.

If methadone prescribing is appropriate, then it should be introduced in a systematic regimen based on reported use, but titrated against objective withdrawal symptoms.

2. What are the main factors to be aware of during the methadone initiation and stabilization period?

Methadone as a treatment has been shown to be beneficial on a number of outcome measures, including reduced incidence of fatal overdose in drug users (Caplehorn et al, 1996; Zador et al, 1997), reduced transmission of HIV, reduced rates of crime, and improved health and life expectancy (Gossop et al, 1997; Strang et al, 1997; Marsch, 1998).

However, the first two weeks of induction into methadone treatment are an important period for overdose

risk and there have been a number of reports of deaths occurring during this time (Drummer, 1992; Harding-Pink, 1993; Caplehorn, 1998; Zador and Sunjic, 2000). Poor or incomplete assessment of opiate tolerance can result in inappropriately high doses being prescribed or, worse still, methadone being prescribed for non-tolerant individuals. This is particularly important as methadone has a long half-life (mean 35 hours: Wolff et al, 2000) leading to a lag time of around seven to nine days to reach steady state serum levels, which may result in cumulative toxicity. The patient may appear to be tolerating methadone well on days one and two but by day seven symptoms of overdose may be apparent.

Polysubstance misuse, when combinations of substances (particularly opiates, alcohol and benzodiazepines) are taken together, is probably one of the main causes of fatal overdose (Farrell et al, 1996). These substances, along with other central nervous system (CNS) depressant drugs, taken in conjunction with methadone can have an additive or synergystic effect, causing fatal respiratory depression (White and Irvine, 1999; AHFS, 2000) and are frequently implicated in polysubstance overdoses with methadone (Drummer et al, 1992; Harding-Pink, 1993; Cairns et al, 1996; Neale, 2000; Zadar and Sunjic, 2000). Polypharmacy is more likely to be associated with more severe social and psychiatric problems, hence increasing the risk of deliberate and accidental overdose (Farrell et al, 1996).

Importantly, an individual's tolerance to opiates can be reduced within days of not taking the drug (Preston, 1996). A particularly high-risk overdose period is the first few weeks following release from prison (Seaman et al, 1998). Another risk period is relapse following detoxification when the patient's tolerance is likely to have been affected.

Inappropriately high dosing can result in potentially fatal overdose, particularly in the first few days. It is safer to keep to a low dose that can subsequently be increased at intervals if this dose later proves to be insufficient. Conversion tables for opiates should be viewed cautiously, as there are a number of factors influencing the values at any given time, particularly with regards to the composition and purity of illicit drugs. Additionally, the

evidence base for opiate conversions in addiction is limited, therefore it is much safer to titrate the dose against presenting withdrawal symptoms. At this stage, an explanation to the patient of what they might expect and the time taken to stabilize the dose is important.

Starting doses should generally be in the range of 10–30 mg, which can then be increased by 5–10 mg daily over the following two to three days. (A second dose of between 5 and 20 mg may be given on the first day, after a minimum interval of four hours, but only if withdrawal symptoms are persistently severe. This should only be done in situations where there are facilities to supervise consumption of methadone and monitor the patient for signs of intoxication for a few hours following ingestion.) The dose should then be reviewed at weekly intervals and increased by increments, no greater than 10 mg at a time (each week), until the patient is stabilized and comfortable. No changes to the dose should be made without assessing the patient. Patients should, at a minimum, be seen at day three or four and again after one week to monitor for signs of toxicity or withdrawal; the dispensing pharmacist should also be vigilant in this respect. These dosage recommendations are in line with current UK Government Clinical Guidelines (1999) for treating opiate dependence within the UK context of substance misuse.

The UK Government Clinical Guidelines (1999) suggest there may be greater benefit in prescribing a daily dose of between 60 and 120 mg methadone for maintenance treatment. One study, in the USA, that randomized users to receive 30 mg of methadone or 80 mg of methadone or buprenorphine, found that those who received the higher dose of methadone were more likely to stay in treatment and less likely to return to using street drugs (Ling et al, 1996). It should be noted that in the USA all methadone is dispensed under supervised conditions; this is not the case in the UK, resulting in a considerably greater risk of prescribed methadone being diverted onto the street for illicit use. The appropriate maintenance dose of methadone for any patient must be based on individual requirements following a careful induction and stabilization period. It is likely that a daily dose of less than 60 mg methadone will be adequate for many individuals with lower tolerance, whereas a daily dose of

methadone more than 20 mg may be necessary for certain individuals with high tolerance levels.

The appropriate duration of methadone maintenance treatment should be based on an individual's needs and may vary from a few months to years. 'Detoxing' a patient when they are not ready may have detrimental effects, including relapse to illicit drug use, increased risk of overdose, a sense of failure, and an adverse impact on psychological and social well-being. Methadone maintenance should not be regarded as a period of inertia, but rather as an opportunity for psychological, social and other general healthcare interventions to be made, whilst drug use remains stable. The purpose is to not attempt to implement too many changes for the individual to have to deal with at once.

Methadone should be supplied in the oral liquid formulation; tablets should not be prescribed as they are likely to be crushed and injected. Ampoules for injection should only be prescribed by specialist practitioners in very specific circumstances.

The UK Government recommends daily supervised consumption of methadone for the first three months of treatment in order to facilitate healthcare, monitor for signs of toxicity and prevent diversion. This can then be reviewed and assessed with regard to the patient's level of stability and compliance (Department of Health Guidelines, 1999). No more than one week's supply of drug should be issued at one time, except in exceptional circumstances. Prescribers and dispensing pharmacists should liaise regularly about the patient and the drug regime.

3. What significant drug interactions need to be considered?

It is important to find out about all drugs used - illicit, prescribed and over-the-counter medications. The most important interactions regarding methadone are those with other CNS depressant drugs that add to the effect of methadone and significantly increase overdose risk, e.g. benzodiazepines, alcohol and other opiates.

Metabolism of methadone to its inactive primary metabolite is mediated mainly by CYP3A4, an enzyme from the cytochrome p450 subfamily of hepatic enzyme systems (Iribane et al, 1996, 1997). Any drug that affects this enzyme (inducer or inhibitor) has the potential to interact with methadone.

The most significant interaction is likely to be with rifampicin, which causes reduced plasma methadone levels in all patients (Raistrick et al, 1996). Methadone doses should be titrated up to abolish withdrawal symptoms (in severe cases doses may need to be doubled), and then carefully titrated down at the end of rifampicin treatment. Other examples of interacting drugs include carbamazapine (reduced methadone levels), fluvoxamine (increased methadone levels) and omeprazole (increased methadone levels). A comprehensive table of interactions can be found in the Department of Health Clinical Guidelines (1999).

4. What plans should be implemented for continuing treatment?

Once the patient is stabilized on methadone other issues can be approached, e.g. does the patient wish to be maintained on methadone for a period of time or are they motivated and ready for a detoxification? Decisions should be taken around who will provide treatment and shared-care arrangements should be set up between primary and secondary care, including other professionals such as community pharmacists.

Other medical issues to consider include:

- Hepatitis and HIV screening.
- Hepatitis A/B vaccination programme.
- Safer sex information.
- Mental health.
- General health and dietary information and advice.

Psychosocial interventions to consider include:

- Motivational enhancement therapy.
- Relapse prevention.
- Family therapy.
- Coping skills.
- Housing and benefits advice.

Key points

- Full assessment is essential to establish a diagnosis of substance misuse and the nature and extent of the patient's drug-related problems.
- Substitute (methadone) prescribing should not be initiated without convincing evidence of current dependence.
- Substitute prescribing should be part of a treatment plan that includes medical, psychological

and social interventions to meet the patient's needs.

- The initial two weeks of treatment with methadone are a high-risk period for methadone overdose, particularly as a result of cumulative toxicity.
- The initial starting dose of methadone should be between 10 and 30 mg. Further increases can be made in increments of 5–10 mg daily for a further two to three days and then weekly. Changes in dose should only be made after assessment and titration against presenting withdrawal symptoms.
- At minimum, the patient should be assessed after three or four days of starting methadone and then after one week to monitor for toxicity.
- Methadone should be dispensed daily to the patient (ideally supervised consumption) for at least the first three months of treatment.
- Oral liquid formulations should be prescribed as tablets are liable to be crushed and injected. Ampoules for injection should only be prescribed by specialists and in exceptional circumstances.
- Prescribers and dispensing pharmacists should liaise regularly about the patient's regime.
- CNS depressant drugs (including alcohol) taken concurrently with methadone can result in a potentially fatal overdose.
- Methadone is primarily metabolized by CYP3A4: other prescribed drugs that inhibit or induce this enzyme may significantly alter methadone requirements.
- For the long-term treatment of substance dependence a multiprofessional approach should be adopted, taking into consideration the patient's individual needs.

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33

Eating disorder – anorexia nervosa

Celia Feetam

SB, a 19-year-old girl, was referred by her GP to a specialist unit. On examination she was found to have a body mass index (BMI: calculated as weight in kilograms divided by the square of the height in metres) of 13. In addition, haematological and biochemical investigations highlighted the following abnormalities:

Serum potassium	*3.0 mmol/l (reference range 3.3–5.8)*
Serum sodium	*129 mmol/l (reference range 130–150)*
Haemoglobin	*11 g/l (reference range 13.5–18.0)*
ALT	*59 IU/l (reference <40)*
Gamma GT	*681 IU/l (reference <40)*

When interviewed by the doctor SB complained of lethargy. She said she was always cold, often had abdominal pain and was constipated. SB refused to discuss food, insisting that she didn't need to eat much because she put on weight so readily. SB

had not menstruated for six months, her hair was fine and lifeless, and her skin looked pale and dry. Physical examination revealed hypotension and bradycardia but SB would not, at this stage, allow the doctor to examine her further.

A urine screen confirmed recent laxative use but there was no history of alcohol or substance misuse, and no evidence of any recent self-injurious behaviour.

An ECG showed the following changes:

- *Sinus bradycardia*
- *Prolonged QT interval*
- *T-wave changes*
- *A reduced amplitude of QRS complex*
- *U waves*

SB had a normal birth and development and was described as being a happy child until her parents separated when she was 12. She did not cope well with puberty. Her parents offered little support at the time as they were preoccupied with their own bitter dispute. SB became preoccupied with food, controlling her weight and calorie intake in a way she could not control other areas of her life. Her parents were powerless to intervene and had become increasingly concerned about SB's physical health. The GP's diagnosis of anorexia nervosa was confirmed and it was decided to admit SB for further assessment.

Questions

1. What might have contributed to SB's abnormal biochemical and haematological test results, and the findings on physical examination?
2. What are the long- and short-term risks of the main metabolic disturbances seen in anorexia nervosa?
3. What, if any, pharmacological therapies, may help SB and what special considerations must be taken into account?

Answers

1. What might have contributed to SB's abnormal biochemical and haematological test results, and the findings on physical examination?

A patient with anorexia nervosa is at risk of a wide range of physical problems that require prompt diagnosis, appropriate investigation and skilled management. Water and salt loss from self-induced vomiting, and excessive diuretic and laxative use may result in dehydration and hyponatraemia (sodium <130 mmol/l). Hyponatraemia may also be the result of water intoxication secondary to excessive drinking. Excessive water intake may be an attempt to mitigate hunger, a form of purging behaviour or a quick means of gaining weight prior to being weighed. Diuretic and laxative misuse (including the use of liquorice) and forced vomiting can also cause hypokalaemia (potassium <3.4 mmol/l) by a variety of mechanisms, including gastric loss and secondary hyperaldosteronism (Greenfield et al, 1995). If hypokalaemia does not resolve with potassium supplements then hypomagnesaemia should also be suspected (Weisinger and Bellorini-Font, 1998).

SB's iron deficiency anaemia is likely to be due to reduced dietary intake of iron but may have been exacerbated by colonic or rectal bleeding as a result of chronic laxative misuse. Leucopenia is also common in anorexia nervosa, giving rise to an increased risk of infection (Palla and Litt, 1988).

Abnormal liver enzymes have been reported in up to 45% of patients with anorexia nervosa (Milner et al, 1985). Transaminase levels are usually raised and bilirubin can be elevated. Fatty infiltration of the liver is known to complicate starvation (Doherty et al, 1991) and could be a factor in the hepatic dysfunction seen in anorexia nervosa. Since deliberate self-harm commonly accompanies eating disorders the possibility of liver damage due to paracetamol overdose should not be discounted.

Anorexia nervosa may affect the structure and function of the heart in a number of ways. Sinus bradycardia and hypotension are common and reflect the adaptive metabolic effects of starvation. Loss of cardiac muscle mass can result in ECG changes which may be exacerbated by various electrolyte disturbances, especially

hypomagnesaemia and hypokalaemia (Palla and Litt, 1988), perhaps leading to prolongation of QT interval.

SB's abdominal pain is probably caused by constipation as a result of a reduced fluid intake and a poor diet combined with laxative abuse. Her tiredness and lethargy may be depressive symptoms, depression is commonly associated with eating disorders or it may be a result of her anaemia.

Localized or generalized dryness of the skin has been reported in 57–97% of patients with anorexia nervosa and occurs at the time of greatest weight loss (Schulze et al, 1999). Dry skin may be associated with reduced levels of thyroid-stimulating hormone or triiodothyronine but can occur in the presence of normal thyroid function. Other related symptoms include split and dry hair, brittle nails and delayed healing, which may also reflect calcium, zinc or other vitamin and trace element deficiency.

Amenorrhoea in anorexia nervosa is associated with decreased gonadotrophin levels and a diminished response to luteinizing hormone releasing hormone (Beumont et al, 1976). Frisch and McArthur (1974) proposed that menarche in humans is dependent on achieving a certain body weight that represents a critical percentage of body fat. In starvation, loss of body fat results in amenorrhoea. Possible mechanisms may include the conversion of androgens to oestrogens by adipose tissue, the influence of body fat on the formation of more potent from less potent oestrogens and the fact that adipose tissue is a source of steroid hormones.

2. What are the long- and short-term risks of the main metabolic disturbances seen in anorexia nervosa?

The chronic course of anorexia nervosa results in significant morbidity and mortality (Beumont et al, 1993). Cardiac complications and abnormalities are common causes of death in anorexia and may be preventable (Neumaker, 1997). Some are the result of electrolyte disturbances secondary to vomiting and laxative abuse, while others are the result of a direct effect of malnutrition on the heart (Bloom et al, 1996). Prolongation of the QT interval is the most significant ECG abnormality because it is a thought to be a risk factor for the development of ventricular arrhythmias and sudden death (Day et al, 1990). Prolongation of

QT interval may be caused or exacerbated by hypokalaemia, hypomagnesaemia or hypocalcaemia but may also occur in the presence of normal electrolyte levels.

Muscle weakness, absent reflexes and tetany are also symptoms of hypokalaemia, while hyponatraemia may cause headache, confusion, restlessness, ataxia, myoclonic jerks, seizures and, eventually, coma.

Deficiency of some vitamins, especially those of the B group, can also cause neurological symptoms such as muscle weakness.

Osteopenia and osteoporosis are common medical complications of anorexia nervosa. Patients like SB often fail to reach their peak bone mass because of the early onset of the eating disorder and the premature and increased bone destruction that occurs during the course of the illness. The greatest risk factor for osteoporosis is oestrogen deficiency, which also manifests as amenorrhoea. There is some doubt as to how far osteoporosis can be expected to improve on the restoration of normal weight. Golden et al (1997) has shown that persisting amenorrhoea in weight-restored adolescents continues to be associated with decreased levels of oestradiol, a continuing risk factor for osteoporosis.

3. What, if any, pharmacological therapies, may help SB and what special considerations must be taken into account?

Any drug treatment in anorexia nervosa has to take account of the primary problem of low BMI as well as any secondary complications. Low BMI, variable absorption of orally administered drugs, possible reduced hepatic and renal function, electrolyte disturbance and cardiovascular problems may all limit drug choice and necessitate careful adjustment of dosage.

Anorexia nervosa is frequently associated with anxiety and depression. Psychotic features may present at low weight as a complication of starvation or during the initial stages of refeeding.

If an antipsychotic in low dosage is considered for the treatment of psychotic features or anxiety and agitation, one with minimal potential to prolong the QT interval (in view of the potential ECG changes associated with the disorder) and elevate prolactin (so as not to further compromise the risk

of osteoporosis) would be the best choice. Whilst antipsychotic-induced weight gain may superficially appear to be advantageous, in practice such drug-induced weight gain is unlikely to be acceptable to the patient and thus may have negative effects on both compliance and future progress.

Although antidepressants are indicated if depressive symptoms are present, there is little evidence to support their use to increase the rate of weight gain in anorexia nervosa. In a small double-blind, placebo-controlled trial involving 35 anorexic patients who had already gained weight, 63% of those randomized to receive fluoxetine maintained a healthy body weight one year after discharge compared to only 16% randomized to the placebo arm. From this it would appear that selective serotonin reuptake inhibitors (SSRIs) may be effective in preventing relapse after weight restoration in anorexia and, furthermore, patients in this trial with a good response showed a reduction in obsessionality and in eating disorder symptoms, as well as an improvement in mood (Kaye et al, 1996).

Special attention should be paid to the correction of electrolyte disturbances, especially hypokalaemia. Oral therapy is to be preferred and, even when severe, conservative management is best in view of the risk of dangerous depletion of calcium, magnesium and phosphate if potassium levels are restored to normal too rapidly (Palla and Litt, 1988). Dietary replacement, if possible, with potassium-rich foods such as bananas may be sufficient.

Many anorexic patients suffer from delayed gastric emptying. Domperidone is preferable to metoclopramide as therapy as it does not cross the blood-brain barrier. Constipation may continue to be a problem, in which case the regular use of a small dose of a gentle bulk laxative may be considered appropriate. In cases where chronic laxative abuse has resulted in impairment of colonic functioning the occasional stimulant or osmotic laxative may be necessary.

Many of the dermatological effects seen in anorexia nervosa could be attributed to vitamin and mineral deficiency, however, clinical studies indicate that vitamin deficiency states are not common in this disorder (Schulze et al, 1999). However, serum levels may not always accurately reflect tissue levels and many anorexic patients take

vitamin supplements in acknowledgement of their inadequate food intake. A general multivitamin and trace element preparation on a daily basis would therefore seem appropriate.

There is considerable controversy over the efficacy of calcium and vitamin D supplements, biophosphonates or oestrogen replacement therapy in the prophylaxis of osteoporosis in anorexic patients. Hormone replacement therapy (HRT) and biophosphonates are not licensed in this population. Klibanski et al (1995) showed that HRT did not reverse the profound osteopenia seen in all young women with anorexia. Trabecular bone loss is severe and may progress despite oestrogen therapy. Significant improvement in bone mass was, however, seen in those young women who had recovered from anorexia nervosa and had resumed normal menstrual function.

There is little evidence that medication improves the course or delays the progression of anorexia nervosa. However, careful choice of medication can ameliorate the somatic symptoms of malnutrition as well as some of the associated psychiatric features, thus facilitating the vital psychological approaches that offer the best chance of improving outcome (Treasure et al, 1995).

Key points

- Anorexia nervosa can result in a wide range of physical problems that require prompt diagnosis, appropriate investigation and skilled management
- The chronic course of anorexia nervosa results in significant morbidity and mortality
- Cardiac complications and abnormalities are common causes of death in anorexia and can be prevented
- Any pharmacological treatment considered appropriate must be used judiciously in order to minimise risks
- Whilst there is little evidence that medication improves the course or delays the progression of anorexia nervosa, careful use of medication can ameliorate the somatic symptoms and some of the associated psychiatric features of this disorder, thus facilitating the vital psychological strategies that offer the best outcome.

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34

Sleep disturbance

Lynn Haygarth

AB, a 71-year-old woman, was referred to the psychiatric day hospital for assessment and treatment of insomnia. She lives with her married son and his two young children in a small three-bedroomed flat. Although AB tries to be quiet at night, her cramped living conditions mean that it is inevitable that she will disturb others. As a result, the family are finding it increasingly difficult to cope. AB complains of being tired and goes to bed at about 10.00 pm but then gets up at between 2 and 3 am. AB also suffers from a peptic ulcer.

AB's current medication is:

Nitrazepam	*7.5 mg nocte (recently reduced from 10 mg nocte)*
Lactulose	*20 ml bd*
Thyroxine	*75 μg mane*
Omeprazole	*20 mg mane*

Nitrazepam was first prescribed three years ago and AB was identified as receiving chronic

treatment. A reducing regimen was prescribed. AB's son believed this to be the cause of her current problems.

On admission to the day hospital, AB's routine blood tests were within accepted ranges of normal.

On arrival at the day hospital, AB would be restless, agitated and reluctant to join in any of the activities. However, in the afternoon she became more settled and could sometimes be observed taking a nap.

Questions

1. Which factors should be considered when treating sleep disturbance?
2. Discuss the appropriateness of AB's past treatment with a hypnotic.
3. Should the nitrazepam be discontinued?

Answers

1. Which factors should be considered when treating sleep disturbance?

A patient complaining of insomnia may present with one or more of the following: difficulty dropping off to sleep, frequent night-time wakening, early morning wakening, daytime sleepiness and general loss of well-being. In the case of AB, the primary problem is early morning wakening.

Estimates of the prevalence of insomnia can vary widely, depending on its definition and on the population studied. Rates of 10–20% are usual but rates of >30% have been reported, particularly in the elderly (Mellinger et al, 1985; Ohayon et al, 1997). Causes of sleep disturbance can vary widely. The first step towards improving the sleep pattern is to establish and treat the primary cause(s). A way of identifying these can be through the system of 'five Ps' – physical,

physiological, psychological, psychiatric and pharmacological - as identified by Lader (1992).

- Physical - e.g. acute or chronic pain, cardiovascular disease, endocrine disturbances, respiratory disease, tinnitus, Parkinson's disease, myalgic encephalitis, myoclonus, restless legs, cramps, sleep apnoea syndrome, nocturia, pregnancy.
- Physiological - e.g. external stimulation (snoring partner, strange bed), disruption of circadian rhythm (jet lag, shift work), late night exercise or heavy meals, increasing age.
- Psychological - e.g. emotional factors (stress tension, grief, anger), abnormal concern about sleeping.
- Psychiatric - e.g. affective disorder (depression, hypomania, mania), psychosis, dementia, anxiety disorder. Nowell et al (1997) found that psychiatric symptoms were a contributing factor in 77% of patients who received a diagnosis of primary insomnia, with depressive symptoms being most prevalent.
- Pharmacological - e.g. CNS stimulants (including caffeine, nicotine, Ecstasy), withdrawal of CNS depressants (including opiates, alcohol and benzodiazepines), cimetidine, clonidine, beta blockers, corticosteroids.

It is important to establish any primary cause for the sleep disturbance and treat this if possible. In the case of AB, pain secondary to her peptic ulcer should be ruled out. Depressive illness and the onset of dementia should also be excluded in AB. AB should have a full assessment of her physical and mental state.

For many patients who complain of insomnia, sleep can be improved by sleep hygiene measures (Ashton, 1997). The length of total sleep varies greatly between normal subjects, with an average of seven to eight hours in adults, although some manage on much less. The length of total sleep is reduced in the elderly to around six hours in the over seventies and increased daytime napping reduces night-time sleep still further.

It is useful to consider the following recommendations:

- Restrict caffeine intake in the evening (sensitivity to caffeine increases with age).
- Only have small amounts of alcohol

(although it is a CNS depressant, excess alcohol interferes with sleep pattern and is a diuretic).
- Reduce smoking, particularly before bedtime (nicotine is a stimulant).
- Avoid late night meals.
- Have light exercise daily but avoid vigorous late night exercise.
- Establish a pattern of going to bed and getting up at the same time daily, avoiding daytime naps.
- Use anxiety management/relaxation principles (Gillegan, 1995).

The primary cause of the sleep disturbance should be treated and sleep hygiene measures introducted.

AB and her son need to be given information on sleep and sleep disturbance, including a copy of the *Good Sleep Guide*; useful written information is also available from the Scottish Medicines Resource Centre (Gillegan, 1995). Emphasis should be placed on the reduced need for sleep with advancing age, the importance of a regular pattern of going to bed and rising, and the necessity to avoid daytime naps.

2. Discuss the appropriateness of AB's past treatment with a hypnotic.

Nitrazepam is a benzodiazepine hypnotic. Benzodiazepines and related drugs are the most widely used hypnotics currently available. From the 1960s they largely superseded the barbiturates and chloral because of their safer side-effect and toxicity profiles, and hopes for a lower dependence potential.

Benzodiazepines are initially very efficient in inducing and prolonging sleep but tolerance to these effects develops. As well as increasing the total sleep time the benzodiazepines also affect the normal sleep pattern (Ashton, 1994).

Sleep consists of five stages that can be divided into two physiological states, known as paradoxical rapid eye movement (REM) sleep and quiet non-rapid eye movement (non-REM) sleep. The quiet sleep is divided into four stages, with progressive relaxation of the muscles and slower and more regular breathing as the sleep moves from stage 1 of light sleep to stage 2, the first stage of deep sleep, to stages 3 and 4 (also known as slow-wave sleep). During REM sleep there is a complete loss of muscle tone and

frequent rapid eye movements. Dreaming is reported to take place in this phase of sleep (Wilson and Nutt, 2000). Sleep cycles are of around 90–100 minutes duration, ending in REM sleep. The amount of time spent in each stage of sleep varies. REM sleep is typically short, with each cycle normally lasting between 5 and 10 minutes and this duration increasing as the night progresses. REM sleep is therefore concentrated in the last third of the night (Shneerson, 2000).

The benzodiazepines alter the normal sleep pattern by reducing the amount of slow-wave and REM sleep but increasing the amount of sleep time overall, with a prolonged amount of light sleep. The effects of benzodiazepines are mediated through GABA by binding to a specific site, the benzodiazepine receptor, located on the GABA-A-chloride receptor complex. Subtypes of benzodiazepine receptors have been identified, the significance of which is uncertain, but BZ1 receptors may be involved in sedation and BZ2 receptors may mediate cognition and memory (Shneerson, 2000).

Although benzodiazepines have a place in the treatment of some forms of epilepsy, severe muscle spasm, acute behavioural disturbance and as a premedication in some surgical procedures, the vast majority of prescriptions are written for their hypnotic and anxiolytic effects. When used as hypnotics, a clinical effect is usually apparent within one hour and peak plasma levels usually occur between one and three hours after ingestion.

Nitrazepam has a long half-life (18–36 hours, extended to 40 hours in the elderly). There is therefore potential for both accumulation on chronic dosing and hangover daytime sedation, making it particularly inappropriate for elderly patients. These findings are not new; Adam et al (1976) reported problems on withdrawal of nitrazepam and Castelden et al (1977) gave evidence for increased sensitivity to nitrazepam in the elderly.

Guidelines recommend that benzodiazepines should be used to treat insomnia only when it is severe, disabling or subjecting the individual to severe distress (CSM, 1988; Russell and Lader, 1992). Long-term chronic use is not recommended. Use of benzodiazepines should be short term and preferably intermittent (BNF 40,

2001). Patients and their carers should be made aware at the beginning of treatment that the therapeutic effects are likely to be short-lived.

It may have been appropriate three years ago to prescribe AB short-term treatment with a hypnotic. However, all available hypnotics can produce tolerance and carry the risk of withdrawal effects (including rebound insomnia) if used regularly for more than a few weeks. The summary of product characteristics (SPC) for nitrazepam recommends 5 mg before retiring as the maximum daily dose in the elderly for not more than four weeks. Therefore, the prescription of nitrazepam at 10 mg for three years does not appear to be the most appropriate choice of treatment.

A more suitable choice for this patient might be intermittent use of a benzodiazepine with a shorter half-life, e.g. loprazolam in a dose of up to 1 mg or lormetazepam in a dose of up to 1.5 mg on retiring (Ashton, 1997). Temazepam is no longer thought to be a suitable hypnotic as it is widely used nationally as a drug of abuse (Anon, 1997). Information on the half-lives and relative effects of the hypnotics are given in the psychotropic drug directory (Bazire, 2000). Although short half-life drugs are less likely to accumulate and cause daytime sedation, their use is no less likely to be associated with falls and hip fractures in the elderly (Wang et al, 2001). Patients prescribed benzodiazepines, irrespective of the half-life of the drug, are twice as likely to suffer a hip fracture than patients not receiving benzodiazepines.

Zopiclone and zolpidem may also be considered as suitable alternative hypnotics again for short-term intermittent use only. Zopiclone has a half-life of 3.5–6 hours and so should cause a low incidence of daytime drowsiness. However, hangover effect is undoubtedly important in some patients and zopiclone use has been associated with an increased risk of being involved in a road traffic accident (Barbone et al, 1998). Zopiclone is less likely than the benzodiazepines to disturb the sleep pattern. The recommended dose range is 3.75–7.5 mg; doses >7.5 mg do not show an increased clinical benefit. Zopiclone mediates its effect via the GABA-A receptor complex but at a different binding site to the benzodiazepines (Noble et al, 1998).

Physical dependence has been reported (Jones and Sullivan, 1998).

Zolpidem has a half-life of around two hours and is also associated with a low incidence of daytime drowsiness. It is rapidly absorbed, giving an effect within 30 minutes that lasts up to six hours. The recommended dose range is 5–10 mg. In the elderly, 5 mg should be used initially. It binds preferentially to only one of the benzodiazepine receptors (Langtry and Benfield, 1990). Initially, it was thought that these newer hypnotics would be unlikely to cause dependence but there are increasing case reports of escalating doses, dependence and withdrawal problems in vulnerable patients (Sullivan et al, 1995; Clee et al, 1996; Ravinshankar and Carnwath, 1998).

Zaleplon is selective for the BZ1 receptor and has a half-life of around one hour. It significantly reduces the time taken to fall asleep in patients who experience initial insomnia. In addition, it has been shown to improve sleep efficiency over four hours, but not eight hours (Dooley and Plosker, 2000). Although Zaleplon is a short-acting hypnotic that is unlikely to accumulate, it is not an appropriate choice for AB as it is unsuitable for patients with early morning awakening.

There are more recognized adverse effects with chlormethiazole and chloral derivatives and neither of these would be suitable choices for AB. Antihistamines are available over the counter for the short-term treatment of insomnia. So far, they are not thought to be as efficacious as benzodiazepines. In addition, they normally have long half-lives, resulting in daytime drowsiness. Herbal remedies, e.g. valerian, and other non-prescription products, e.g. melatonin, are also widely used hypnotics (Wagner et al, 1998).

In conclusion, if other interventions to improve the sleep pattern have failed and if a hypnotic is to be prescribed, the lowest dose should be given for the shortest period of time. Intermittent use is preferable. Patients should be informed of the interaction between hypnotics and other sedative drugs or alcohol. Impairment of daytime performance should be anticipated, particularly if the patient drives a car. Short half-life hypnotics are no less likely to lead to falls in the elderly than long half-life drugs.

3. Should AB's nitrazepam be discontinued?

Before considering withdrawal of the nitrazepam in AB it is necessary to

identify and treat any physical or psychological cause of her sleep disturbance. In addition, sleep hygiene measures need to be introduced. Tolerance to the effect of nitrazepam has probably occurred and the recent reduction in dose could have resulted in some rebound insomnia. The family will therefore be likely to show some resistance to withdrawing the hypnotic as previous attempts to do this were linked to increased sleep disturbance. Many patients who have taken benzodiazepine hypnotics nightly for years, given regular support and encouragement, can have the drugs withdrawn successfully (Jones, 1990/91). If withdrawal is to be attempted it should be slow and planned, and information on the process given to the patient and carers.

On withdrawal of benzodiazepines the most common problem is an increase in the original complaint (in this case sleep disturbance). Other symptoms may be physical, e.g. dry mouth, sweating, lethargy, headache and nausea, or mental, e.g. impaired memory and concentration. More serious symptoms include perceptual changes, flu-like symptoms, anorexia, sore eyes, depression and abnormal sensations of movement. Rarely, convulsions, psychoses and delusions have occurred. The symptoms can be minimized by using a slow withdrawal. For benzodiazepine withdrawal it is usual to recommend changing the prescribed benzodiazepine to one with a long half-life, normally diazepam, and then withdraw slowly over two to three months (Ashton, 1994). However, it is also reasonable to consider a gradual reduction of the nitrazepam, as it has a long half-life and is less likely to cause withdrawal problems than a shorter acting hypnotic. Using a liquid preparation, reductions of 1 mg could be made every one to two weeks, reducing to 0.5 mg reductions when lower doses, e.g. 4 mg, are reached. Some patients are unwilling to withdraw and this should not be forced, particularly in the elderly, as success is unlikely if the patient is not motivated to change.

If a hypnotic is prescribed in the future it is important that it has a short half-life and is only prescribed for short-term intermittent use. There is no evidence to advocate the use of any medication to assist in withdrawal from benzodiazepines.

Key points

- The primary cause of the sleep disturbance should be identified and treated wherever possible.
- Hypnotics should only be prescribed for short-term treatment of insomnia.
- When prescribed, hypnotics should be used intermittently.
- Benzodiazepines with long half-lives are inappropriate for the elderly as they may accumulate.
- Understanding sleep requirements is important.
- Good sleep hygiene should be encouraged.
- Benzodiazepine withdrawal should be agreed, planned and done slowly.

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35

Complementary therapies

Sarah Beck

BJ is a 46-year-old, married lady who presented to her GP complaining of feeling 'a bit down' recently. For the last two months she has felt quite tearful much of the time and found it difficult to get going in the mornings. She has also been finding it difficult to cope with the housework and the moods of her teenage sons, aged 14 and 17. She reported no problems with sleep, but complained of reduced appetite and thought she might have lost some weight.

BJ has a part-time job in the local library which she usually enjoys but has recently lost interest in the work and finds dealing with the public quite stressful.

BJ had one similar episode 12 years ago when her children were small. She made a good recovery with imipramine 75 mg bd but suffered from constipation, dry mouth and dizziness. She is reluctant to take 'drugs' again and would like to

try a 'more natural' remedy. A friend has suggested she try St John's Wort because she has heard it is good for depression and does not have any side-effects.

Questions

1. Is St John's Wort a suitable choice of antidepressant for BJ?
2. BJ's mother has also been experiencing some 'memory problems' recently and has heard that *Ginkgo biloba* would help. BJ asked if this was true?
3. Is there a role for complementary therapies in psychiatry?

Answers

1. Is St John's Wort a suitable choice of antidepressant for BJ?

St John's Wort (SJW) is the popular name for a plant called *Hypericum perforatum* that has traditionally been used as a treatment for insomnia, anxiety and depression. It contains a number of compounds that include hypericins and flavonoids. Although several theories have been put forward to explain the mechanism of action of SJW, the identity of the active component remains uncertain. Initially it was thought that hypericin was active in treating depression and this is why most preparations of SJW are standardized according to their total content of hypericins. However, it has since been shown (Cott, 1997) that hypericin has affinity only for *N*-methyl-D-aspartate (NMDA) receptors in vitro. Hypericum, in contrast, has affinity for adenosine, $GABA_A$ and $GABA_B$, and monoamine oxidase (MAO) A and B receptors. Only weak affinity for MAO_A and MAO_B receptors has been demonstrated in vitro, insufficient to account for the observed antidepressant effect in humans. Hypericum inhibits the synaptosomal uptake of serotonin in a similar way to clomipramine (Muller et al, 1997).

It has also been suggested that administration of SJW causes an increased density of 5HT 1A autoreceptors (a property shared by conventional antidepressants) and increased responsiveness of post-synaptic 5HT2A receptors [similar to

that found with electroconvulsive therapy (ECT) and conventional antidepressants] (Teufel-Mayer and Gleitz, 1997). At this time, no firm conclusions can be drawn.

There are many published studies of the use of SJW as an antidepressant, but most contain methodological flaws. For example, none of the studies has lasted longer than eight weeks; different studies used different preparations of SJW with unstandardized ingredients; SJW was often compared with subtherapeutic doses of tricyclic antidepressants (TCAs); and subjects often had only mild to moderate depression. (Mild depression is not usually treated with antidepressant drugs.) SJW has not been compared with the selective serotonin reuptake inhibitors (SSRIs), which are generally better tolerated than TCAs. No studies have looked at the use of SJW for severe depression. In light of these flaws, a meta-analysis (Linde and Mulrow, 1999) and a review (Gaster and Holroyd, 2000) have concluded that SJW may be useful in the treatment of mild to moderate depression, but not for severe depression.

A more recent study (Woelk, 2000) addressed the issue of subtherapeutic doses of comparitor drugs by comparing hypericum extract to a therapeutic dose of imipramine (75 mg bd). Again, patients with severe depression were excluded. The authors concluded that *Hypericum perforatum* was therapeutically equivalent to imipramine in treating mild to moderate depression and that hypericum was better tolerated.

BJ would like a medicine that does not cause side-effects. Complementary medicines are often perceived by the public to be natural and so devoid of side-effects. This may be possible with homeopathic medicines but is not true for herbal remedies like SJW. One analysis found that 26% of patients reported side-effects from SJW compared with 48% from TCAs (Linde and Mulrow, 1999). The most commonly reported side-effects from SJW were dry mouth, nausea, constipation, fatigue, dizziness, headache, restlessness and allergic reactions. In addition, SJW contains a red pigment (hypericin) that can, in very high doses, cause photosensitivity reactions (Bove, 1998). SJW has also been reported to trigger hypomanic episodes in people with a bipolar affective disorder (Nierenberg et al, 1999).

A number of drug interactions between SJW and other medicines have been reported (Ernst, 1999). It is thought that this occurs because SJW induces cytochrome P450 3A4. SJW can significantly reduce plasma concentrations of digoxin and indinavir (Piscitelli et al, 2000) and there have been case reports of SJW lowering the plasma concentrations of theophylline, cyclosporin, warfarin and the combined oral contraceptive pill, sometimes leading to treatment failure (Ernst, 1999). A serotonin syndrome may occur if SJW is taken with SSRIs (Lantz et al, 1999).

The evidence base for SJW should be discussed with BJ. It should be pointed out that SJW is not a licensed preparation in the UK and this means that less is known about its effects and side-effects than for more conventional treatments. SJW is only available as a herbal complementary therapy and it is not usually prescribed in the UK. In general, it is preferable to use treatments that are proven to be effective and where the long-term adverse effects are better known.

An SSRI might be a suitable choice for BJ as it is less likely to cause the anticholinergic and alpha-adrenergic side-effects that she experienced previously with imipramine. If BJ has a strong preference for trying a 'natural remedy' like SJW, this may be facilitated so long as her depression is not severe. She should be followed up closely and observed for any deterioration in her mental state.

2. BJ's mother has also been experiencing some 'memory problems' recently and has heard that* Ginkgo biloba *would help. BJ asked if this was true?

BJ's mother is presenting with memory problems that may be consistent with the onset of a dementing illness. She should be assessed by her GP to confirm the diagnosis and exclude any treatable causes.

Alzheimer's disease (AD), the most common form of dementia, is associated with destruction of cholinergic neurons and low levels of acetylcholine in the brain (Knapp et al, 1998). This observation has led to the development of the cholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine) as treatments. Although donepezil has been available for three years in the UK, funding restrictions have meant that it has not been widely prescribed. This is likely to change following the

recent National Institute for Clinical Excellence (NICE) (2001) guidelines that recommend cholinesterase inhibitors being made available for patients with mid- to moderate AD if certain conditions are met. Further discussion of this point can be found in Chapter 26.

Another theory of the aetiology of AD is that cell membrane lipids and other cell components can be damaged by free radicals, eventually leading to cell death. Antioxidants such as alpha-tocopherol and selegiline have been used as treatments, although evidence of their efficacy is limited.

Ginkgo biloba is a herbal remedy that has been available for the treatment of 'cerebral insufficiency' in Germany since 1965. It is approved for prescription in Germany and is now also commonly used in France (Curtis-Prior et al, 1999). The active components of *Ginkgo biloba* are thought to be flavonoids, terpenoids, ginkgolides, bilobalides and other organic acids. Flavonoids and terpenoids are thought to have antioxidant effects. Ginkgolides have been shown to be antagonists of platelet-activating factor (PAF) and it has been suggested that PAF has a detrimental effect on neuronal function (Oken et al, 1998). Ginkgo may also inhibit MAO_A and MAO_B.

Although a number of empirical trials have been carried out to determine the efficacy of *Ginkgo biloba* for cerebral insufficiency, few trials have used a robust enough method in order to judge its effectiveness. A common problem in interpreting trials for herbal medicines is that a standard extract of the medicine is not usually used. This problem has been overcome for *Ginkgo biloba* by the use of a standard extraction process that produces Egb 761, which must contain 24% w/w flavone glycosides and 6% terpenoids.

The efficacy of *Ginkgo biloba* extract on the cognitive function of patients with AD has been reviewed by Oken et al (1998): only four of 50 studies met all their inclusion criteria. There were 212 subjects in each of the placebo and ginkgo treatment groups. The people in the ginkgo group were given 120–240 mg *Ginkgo biloba* extract daily for three to six months. A 3% difference in the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) subtest in favour of the ginkgo treatment arms was found at endpoint. This was statistically significant

($p < 0.0001$). One of the trials identified (Le Bars et al, 1997) used the ADAS-Cog subtest specifically to assess the effectiveness of *Ginkgo biloba* in dementia. A mean treatment difference of 2.1 points in the AD group was found at 26 weeks. This treatment effect is slightly less than those from a 24-week donepezil trial (Rogers et al, 1998) that found treatment differences of 2.5 and 2.9 with doses of 5 and 10 mg daily, respectively, and a galantamine trial (Tariot et al, 2000) that found treatment differences of 3.3 and 3.6 points at doses of 16 and 24 mg daily, respectively ($p < 0.0001$ versus placebo, both doses), after five months. Both these trials enlisted patients with probable AD.

No significant adverse effects have been associated with *Ginkgo biloba* in the published placebo-controlled trials. There have been case reports of headaches, dizziness, palpitations, allergies and gastrointestinal disturbances (Oken et al, 1998). The consumption of *Ginkgo biloba* has also been associated with a prolonged bleeding time (Oken et al, 1998), so it should be used with caution in patients already taking anticoagulant medication such as aspirin and warfarin. Another possible interaction is with the antidepressant drugs, monoamine oxidase inhibitors (MAOIs) and SSRIs, as *Ginkgo biloba* may inhibit MAO_A and MAO_B.

BJ's mother should be encouraged to discuss her memory problems with her own GP, who will want to confirm the diagnosis and eliminate any treatable causes. The use of both *Ginkgo biloba* and conventional treatments for dementia should be discussed in detail, including all the limitations of such treatments as described above. *Ginkgo biloba* cannot be prescribed in the UK as it does not have a marketing authorization and is available only as a food supplement.

3. Is there a role for complementary therapies in psychiatry?

The term 'complementary therapy' is used to describe a wide range of therapies not considered to be conventional. These therapies are diverse and include homeopathy, herbal remedies, aromatherapy, acupuncture, hypnosis and spiritual healing. Some differ from conventional medicine in that they aim to treat the person as a whole rather than by targeting a specific symptom. The use of complementary therapies has an interesting psychological aetiology. For

example, a group of people with cancer was asked why they used complementary therapies. They said it made them feel more hopeful, they liked the holistic nature, greater participation in care and the practitioner's supportive approach, despite the fact that very few anticipated a cure (Downer et al, 1994). Forty per cent of these patients did not tell their doctor that they were using complementary therapies. Another (postal) survey (Thomas et al, 1991) found that a quarter of patients use conventional and complementary therapies at the same time, especially for atopic conditions, headaches and arthritis.

The area of psychiatry has not been bypassed by an interest in complementary therapies. As well as the two treatments that have already been discussed, there has been much interest in the use of fish oils and evening primrose oil for the treatment of schizophrenia (Joy et al, 1999), but the results are so far inconclusive. Aromatherapy is commonly offered on wards and in day centres.

Those who suffer from mental health problems, particularly depression and anxiety, are even more likely to use complementary therapies than the general population (Kessler et al, 2001). Very few seek advice from a trained practitioner such as a herbalist or aromatherapist. A survey by Kessler et al (2001) found that complementary therapies were perceived to be as helpful as conventional treatments and were used alongside conventional treatments by two-thirds of respondents suffering from anxiety or depression.

Although the UK market for complementary therapies was worth £40 million in 1994, the use of these therapies is largely unregulated. Adverse effects and drug interactions are often not recognized and so go unreported. There is a paucity of controlled trials, products are not subject to licensing requirements and efficacy and adverse effects are poorly evaluated. In the UK there are no regulatory bodies to monitor side-effects and possible drug interactions.

Many people, such as BJ, associate complementary therapies with being 'natural' and 'safe' being unaware that side-effects may occur or that certain treatments should be avoided by some people (eg both evening primrose oil and rosemary should be avoided in

epilepsy). Clinicians need to be proactive in asking patients whether they use any complementary therapies and be willing to discuss the potential benefits and risks. They also need to be aware of the limits of their own worthwhile knowledge. Most complementary therapies require years of study to master.

Key points

- The diverse group of treatments described as 'complementary therapies' are widely used in society.
- The general public regard complementary therapies as 'natural' and 'safe' but are unaware that they can cause side-effects and may interact with conventional treatments.
- Up to 40% of patients do not tell their doctor that they are using complementary therapies.
- St John's Wort may be as effective as TCAs for the treatment of mild to moderate depression but more studies are needed to confirm this. None of the published studies have included patients with severe depression.
- There is some evidence to suggest that *Ginkgo biloba* may be of benefit in Alzheimer's disease; it is less effective than the cholinesterase inhibitors but better tolerated.

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