The 54% of those selected for interview who did not participate may have had very different experiences from those who chose to comply, therefore introducing important responder bias. Using non-independent researchers is likely to bias responses.

The VSSS asks patients to indicate their satisfaction on a five-point Likert scale. The choices are: 1=terrible, 2=mostly unsatisfactory, 3=mixed, 4=mostly satisfactory and 5=excellent. The mean satisfaction scores reported by Leese *et al* are less than four (mostly satisfactory) in all but one domain in both services at both time points. Scores which fall short of mostly satisfactory must indicate that users' experiences of services could have been better. Leese *et al*'s interpretation – that this indicates successful services delivering fairly high levels of satisfaction – ignores the discontent that respondents have expressed.

This potential misreading of patients' experiences is compounded by the use of summary scores only. In our survey of psychiatric in-patients (Greenwood *et al* 1999) we report 73% of patients as very or fairly satisfied. Even in this group 60.4% reported significant levels of adverse experiences with the service. The strength of the VSSS is that it questions the respondents in some detail within each domain. Averaged satisfaction scores may well obscure real dissatisfaction including perhaps a number of unpleasant experiences.

If services are to be evaluated with a view to improving them, then the details of dissatisfaction that users voice may be the most valuable and deserve closest attention.

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Traumatic brain injury and post-traumatic stress disorder

Sir: O'Brien & Nutt (1998) develop the proposition that traumatic brain injury may protect against the development of emotional consequences arising from a traumatic experience (Adler, 1945). Although it may be compelling to think that nightmares or horrific memories associated with such events cannot occur if there has been loss of consciousness, the literature does not support this contention (see review, McMillan, 1997). One study reports on 10 cases who had traumatic brain injury ranging from mild to very severe and had post-traumatic stress disorder (PTSD) (McMillan, 1996). Several ways in which PTSD can develop, despite loss of consciousness and post-traumatic amnesia, have been reported. These include distressing 'windows' in memory, which for minor head injuries includes isolated memories soon before (e.g. of a lorry about to make impact) and after (e.g. being in a car, trapped and smelling petrol) the accident, and for more severe head injuries isolated memories during post-traumatic amnesia (McMillan, 1996). Some suggest that implicit learning which occurs during post-traumatic amnesia is a vehicle (Layton & Wardi-Zonna, 1995). These studies indicate that loss of consciousness and post-traumatic amnesia may not protect an individual from traumatic emotional experiences, but not that this never occurs.

O'Brien & Nutt suggest that by mimicking neurotransmitter changes caused by traumatic brain injury by pharmacological intervention, the development of PTSD might be arrested in people who have sustained no head injury. Given that PTSD occurs even in people who have sustained a severe head injury, and that other emotional consequences such as travel anxiety/phobias are not uncommon, some doubt must be placed upon their premise. Furthermore, traumatic brain injury triggers a cascade of biochemical events resulting in oedema, necrosis, haemorrhage and functional impairment. The complexity of secondary injury processes makes it difficult to elucidate the roles of specific injury mechanisms, including those underlying loss of consciousness and post-traumatic amnesia. Glutamatergic (Faden, 1996; Koura *et al*, 1998) and cholinergic mechanisms (Murdoch *et al*, 1998), each implicated in memory dysfunction, are also postulated to underly coma in man. After traumatic brain injury these and caspase-3-like proteases (Yakovlev *et al*, 1997), endogenous opioids acting on kappa-2 receptors (Faden, 1996) and other acute metabolic responses contribute to coma in experimental animals. It may be premature to pin the pathophysiology of coma or post-traumatic amnesia primarily on glutamatergic mechanisms which are responsible for only a proportion of these post-traumatic sequelae (Myseros & Bullock, 1995). Any pharmacological hypothesis needs to account both for 'windows' of awareness during loss of consciousness and post-trumatic amnesia despite 'excitotoxic surge', and for the registration and consolidation of memories therefrom. As O'Brien & Nutt acknowledge, the pharmacological bases for retrograde and anterograde amnesia are likely to differ, each time frame a potential source of traumatic memories.

Given the present state of knowledge about PTSD after traumatic brain injury, it is premature to recommend the pharmacological intervention of the kind that they suggest for the reasons that they give.

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Author's reply: Thank you for drawing to our attention a number of studies of which we were unaware. The question which arises from these case reports of intrusive traumatic images despite unconsciousness is: why do they occur? Do they reflect an excess level of arousal which overcompensates for the coma, or is the explanation something to do with regionally different effects of the brain trauma? We might presume that sensory stimuli, such as smells, which may have a closer association with anxiety centres in the temporal lobe, could be particularly prone to such remembering and it would be interesting to determine whether there was a preponderance of such cases.

The other point that one should not focus solely on glutamatergic mechanisms in prevention of PTSD is, of course, valid. I thought that we had given a reasonably broad overview of what transmitters might be important and could envisage that a cocktail of therapy designed to effectively modulate both primary excitatory transmission, opiate and noradrenergic inputs might in the long run be most effective for the non-concussed patient. What is important is that people accept that there may be scope for specific interventions here and begin to design trials to test hypotheses and perhaps to provide clinical benefit.

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Orphenadrine

Sir: We read with interest the article by Buckley & McManus (1998). Their findings considering the use of anticholinergic drugs to reduce Parkinsonian symptoms during antipsychotic drug therapy, and in particular the high fatality rate associated with the ingestion of orphenadrine, are supported by several previous reports (Bosche & Mallach, 1969; Blomquist *et al*, 1971; Deceuninck *et al*, 1973; Bozza-Marubini *et al*, 1977; Millar, 1977; Robinson *et al*, 1977; Sangster *et al*, 1978; Wilkinson *et al*, 1983; Clarke *et al*, 1985; Ellenhorn, 1997; Gjerden *et al*, 1998).

In 1997, we conducted a study of the relative toxicity of anticholinergic anti-Parkinsonian drugs in Norway (Gjerden *et al*, 1998). All autopsy samples received at the National Institute of Forensic Toxicology in Oslo during the years 1986–1996 which contained anticholinergic anti-Parkinsonian drugs were reviewed. The National Institute of Forensic Toxicology is a centralised body which receives samples from the entire country and is responsible for toxicological analyses in the vast majority of medico-legal autopsies in Norway.

Blood samples from a total of 69 cases tested positive for drugs of this class. Of the 69, orphenadrine was present in 57 (83%), biperiden in eight (12%), procyclidine in three (4%) and benzhexol (trihexyphenidyl) in one (1%) subject. The measured concentrations were assessed in the light of previously published data. Of 21 cases where causality between drug ingestion and death was classified as either highly probable (18/21) or possible (3/21), the samples contained orphenadrine in concentrations from 4.5 to 600 μmol/l (mean=62.5 μmol/l, s.d.=126.5). The data are summarised in Table 1. Because of a low national autopsy rate (about 7% in 1990, 4.4% in 1994), there is reason to believe that the actual numbers of drug-related deaths in this period may have been significantly higher.

Although the sales data (Table 1) should suggest much lower numbers, orphenadrine was found in 83% of samples which met the inclusion criteria. We have no explanation for this overrepresentation. Also, among the 69 patients who had taken orphenadrine prior to death, more than 50% did not test positive for an antipsychotic agent. This is a deeply troubling finding, which suggests that there may be considerable overconsumption of orphenadrine in Norway.

There is a paucity of pharmacological studies concerning drugs of the anticholinergic anti-Parkinsonian class, and orphenadrine may well be the one best described in the literature. What little we know of its pharmacological properties raises additional questions concerning its use and safety. Orphenadrine is readily absorbed, but approximately 30% of an ingested dose is subjected to pre-systemic metabolism (i.e. the first-pass effect). It is extensively metabolised in the liver and the plasma half-life of the parent compound is reported to be 13–20 hours (Dollery, 1991; Ellenhorn, 1997). However, continuous use, which is the norm rather than the exception, will prolong the half-life to about 30–40 hours. This has been suggested to be due to autoinhibition by a desmethylated metabolite of orphenadrine (Labout *et al*, 1982). Moreover, orphenadrine is a substrate for the cytochrome P450 isoenzyme CYP3A (Cresteil *et al*, 1994), which makes it a likely candidate for pharmakokinetic interactions with a series of antiarrhythmic, anxiolytic and cytotoxic drugs as well as some hormones. Orphenadrine is an inhibitor of CYP2B6 (Chang *et al*, 1993), which is responsible for the biotransformation of xenobiotics as diverse as nicotine and cyclosphamide. At least in theory, orphenadrine may cause a number of unpredictable and complex pharmacological interactions.

Table 1 Autopsy cases during the 11 years 1986–1996 where samples were submitted to the National Institute of Forensic Toxicology, Norway, and where the analytical findings included at least one anticholinergic anti-Parkinsonian drug

	Positive blood sample	Probable death by overdose	Mean yearly sale (DDD[1]/1000/day)	Mean market share (%)
Orphenadrine	57	21	0.53	44.5
Biperiden	8	0	0.23	19.3
Benztropine	0	0	0.09	7.6
Benzhexol	1	0	0.26	21.9
Procyclidine	3	0	0.08	6.7
Total	69	212	1.19	100.0

1. Defined daily dose.

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