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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 over-representation. 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 auto-inhibition 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.

https://doi.org/10.1192/S0007125000262065 Published online by Cambridge University Press

Two other anticholinergic anti-Parkinsonian agents are currently available in Norway, biperiden and benztropine (benzhexol and procyclidine were withdrawn from the market in 1995 and 1996, respectively). The current state of knowledge concerning these other drugs is abysmal; for instance, we have not encountered comprehensive pharmacokinetic studies of any of these compounds. It is, however, notable that there are very few case reports of deaths in association with their use. No deaths, but two intoxications which required hospitalisation, have been described after intake of biperiden (Hewer & Biedert, 1988). A total of five deaths have been reported in the literature in association with benztropine ingestion (Särnquist & Larson, 1973; del Villar & Liddy, 1976; Wade & Ellenor, 1980; Catterson & Martin, 1994). We have not found any reports of acute deaths caused by either benzhexol or procyclidine.

The data presently available show that orphenadrine is associated with a comparably high risk of acute death from overdose. In general, the use of anticholinergic agents to counter side-effects from antipsychotics should be discouraged, but if indicated, several other compounds may be used more safely. The consequences of this should be fairly obvious, but the continuum of high death rates from orphenadrine poisonings seems to demonstrate how difficult it is to change an ill-advised therapeutic tradition.

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The beginning and end of psychiatric pathways

Sir: The article by Lincoln *et al* (1998) made an interesting reading. The understanding of contacts that people make prior to consulting a psychiatrist is a vital factor in planning to reduce the delays in seeking treatment. Based on the results of a multicentre study conducted in India (further details available from the author upon request) with a similar background, we would like to share our experiences.

Elucidating responses on various aspects of the pathways to care may lead to responder bias in the case of patients who are psychotically unstable or with a history of primary memory disorders like amnesia and dementia. Moreover, cross-checking statements from the accompanying key informants or relatives would have enhanced the accuracy of the collected data.

Our study consisted of 396 subjects selected from five geographically and culturally different regions of India. The diagnostic make-up of our sample revealed that a majority of people suffering from either schizophrenia (53.7%) or depression (53.5%) had reached a psychiatrist within a year of onset of symptoms, whereas the group suffering from either acute transient psychosis, substance-related psychosis or other unspecific psychosis reached a psychiatrist much earlier (more than 50% within one month). Although it is difficult to explain this variation, it could be due to the relatively benign prodromal phases of depression and schizophrenia compared with the other group. So far as the first care-givers are concerned, we found that psychiatrists were consulted in 33.7% of the cases which is much higher than that reported by Lincoln *et al* (16.1%).

Finally, it is not clear where exactly the pathways to psychiatric care begin. Do they begin with the family, friends or the patient himself or herself? A similar question remains regarding its end. Does it really end with the psychiatrist? In our study we found that 1–2% of study subjects in different centres consulted further care-givers even after seeing a psychiatrist. Hence, we hypothesise that pathways to psychiatric care are not static events or strategies, but an ongoing process in search of an ideal care-giver. It is a process dependant on a wide range of biopsychosocial factors which need to be understood individually.

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https://doi.org/10.1192/S0007125000262065 Published online by Cambridge University Press