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

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 disturbing ‘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-1-like proteases (Yakovlev et al, 1997), endogenous opioids acting on kappα-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 (Myserson & Bullock, 1995). Any pharmacological hypothesis needs to account both for ‘windows’ of awareness during loss of consciousness and post-traumatic amnesia despite ‘excitotoxic surge’, and for the registration and consolidation of memories theretom. 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.


Activation of CPP32-like caspases contributes to
neuronal apoptosis and neurological dysfunction after
traumatic brain injury Journal of Neurosciences, 17,
7415-7424.

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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 pre-
sume 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 trans-
m ission, 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 sup-
sported by several previous reports (Bosche
& Mallach, 1969; Blomquist et al, 1971;
Decuvinck 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,

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 Toxicol-
yogy 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 major-
ity 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%), procy-
lidine in three (4%) and benzhexol (tri-
hexyphenidyl) in one (1%) subject. The
measured concentrations were assessed in
the light of previously published data. Of
21 cases where causality between drug in-
gestion and death was classified as either
highly probable (18/21) or possible (3/21),
the samples contained orphenadrine in con-
centrations 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 signifi-
cantly higher.

Although the sales data (Table 1)
should suggest much lower numbers,
orphenadrine was found in 83% of sam-
plies which met the inclusion criteria. We
have no explanation for this over-
representation. Also, among the 69 pa-
tients who had taken orphenadrine prior
to death, more than 50% did not test posi-
tive for an antipsychotic agent. This is a
deeply troubling finding, which suggests
that there may be considerable overcon-
sumption of orphenadrine in Norway.

There is a paucity of pharmacological
studies concerning drugs of the anticholin-
ergic anti-Parkinsonian class, and orphen-
adrine may well be the one best described
in the literature. What little we know of
its pharmacological properties raises addi-
tional 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 meta-
bolised 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). More-
over, orphenadrine is a substrate for the cy-
tochrome P450 isoenzyme CYP3A (Cresteil
et al, 1994), which makes it a likely candi-
date 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 cyclophosphamide.
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

<table>
<thead>
<tr>
<th>Positive blood sample</th>
<th>Probable death by overdose</th>
<th>Mean yearly sale (DDD/1000/day)</th>
<th>Mean market share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphenadrine</td>
<td>57</td>
<td>0.53</td>
<td>44.5</td>
</tr>
<tr>
<td>Biperiden</td>
<td>8</td>
<td>0.23</td>
<td>19.3</td>
</tr>
<tr>
<td>Benztropine</td>
<td>0</td>
<td>0.09</td>
<td>7.6</td>
</tr>
<tr>
<td>Benzhexol</td>
<td>1</td>
<td>0.26</td>
<td>21.9</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>3</td>
<td>0.08</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>212</td>
<td>1.19</td>
</tr>
</tbody>
</table>

1. Defined daily dose.