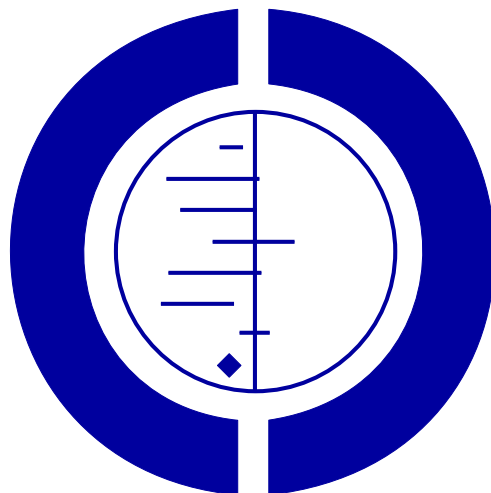


Pharmacological management for agitation and aggression in people with acquired brain injury (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	2
OBJECTIVES	3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	4
METHODS OF THE REVIEW	5
DESCRIPTION OF STUDIES	5
METHODOLOGICAL QUALITY	6
RESULTS	7
DISCUSSION	8
AUTHORS' CONCLUSIONS	9
POTENTIAL CONFLICT OF INTEREST	9
ACKNOWLEDGEMENTS	9
SOURCES OF SUPPORT	9
REFERENCES	10
TABLES	14
Characteristics of included studies	14
Characteristics of excluded studies	16
Characteristics of ongoing studies	20
ADDITIONAL TABLES	21
Table 01. Brookes 1992b (average maximum intensity of agitated episodes)	21
Table 02. Brookes 1992b (average number of agitated episodes)	21
GRAPHS AND OTHER TABLES	21
INDEX TERMS	21
COVER SHEET	21

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ABSTRACT

Background

Of the many psychiatric symptoms that may result from brain injury, agitation and/or aggression are often the most troublesome. It is therefore important to evaluate the efficacy of psychotropic medication used in its management.

Objectives

To evaluate the effects of drugs for agitation and/or aggression following acquired brain injury (ABI).

Search strategy

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and other electronic databases. We also searched the reference lists of included studies and recent reviews. In addition we handsearched the journals *Brain Injury* and the *Journal of Head Trauma Rehabilitation*. There were no language restrictions. The searches were last updated in June 2006.

Selection criteria

Randomised controlled trials (RCTs) that evaluated the efficacy of drugs acting on the central nervous system for agitation and/or aggression, secondary to ABI, in participants over 10 years of age.

Data collection and analysis

We independently extracted data and assessed trial quality. Studies of patients within six months after brain injury and/or in a confusional state, were distinguished from those of patients more than six months post-injury, or who were not confused.

Main results

Six RCTs were identified and included in this review. Four of these evaluated the beta-blockers, propranolol and pindolol, one evaluated the central nervous system stimulant, methylphenidate and one evaluated amantadine, a drug normally used in parkinsonism and related disorders. The best evidence of effectiveness in the management of agitation and/or aggression following ABI was for beta-blockers. Two RCTs found propranolol to be effective (one study early and one late after injury). However, these studies used relatively small numbers, have not been replicated, used large doses, and did not use a global outcome measure or long-term follow-up. Comparing early agitation to late aggression, there was no evidence for a differential drug response. Firm evidence that carbamazepine or valproate is effective in the management of agitation and/or aggression following ABI is lacking.

Authors' conclusions

Numerous drugs have been tried in the management of aggression in ABI but without firm evidence of their efficacy. It is therefore important to choose drugs with few side effects and to monitor their effect. Beta-blockers have the best evidence for efficacy and deserve more attention. The lack of evidence highlights the need for better evaluations of drugs for this important problem.

PLAIN LANGUAGE SUMMARY

To be added.

BACKGROUND

Psychological and psychiatric problems exceed physical problems as causes of morbidity and disability following acquired brain injury (ABI) (Jennett 1981). Of the many psychiatric symptoms that may result from ABI, agitation and aggression are often the most troublesome for carers and patients. Agitation and aggression on medical or surgical wards immediately following the injury occur in about 11% of patients (Brooke 1992a). They can cause disruption to the normal running of the ward and, when a patient returns home, the family may suffer considerable distress (Livingston 1985), resulting from the difficulties of looking after somebody who may now be irritable (Brooks 1987; Thomsen 1984), and occasionally violent (Lezak 1978). There is good evidence that patients with a head injury have an increased risk of aggression and agitation. For example when compared with patients with multiple trauma but without head injury, three times as many head injured patients showed significant aggression during the first 6 months post injury as did the control group (33.7% versus 11.5%) (Tateno 2003). And problems with aggression continue for many years in a proportion of cases. For example a quarter of patients at follow-up six, 24 and 60 months after discharge from an in-patient rehabilitation unit displayed aggressive behaviour (Baguley 2006).

In light of this it is surprising that clinicians are yet to agree on definitions of agitation and aggression (Sandel 1996). A variety of terms are used to refer to agitation and aggression and often the two terms are treated as interchangeable. Although the concept of agitation and aggression are closely intertwined it is useful, both theoretically and practically, to draw a distinction between them.

Agitation, defined as disturbed behaviour as a result of overactivity, occurs frequently in the acute phase of recovery, where it is usually related to post-traumatic amnesia (PTA). Post-traumatic amnesia is a transient period characterised by disorientation, confusion and cognitive impairment. As improvements in cognition tend to precede improvements in agitated behaviour (Corrigan 1988), environmental intervention rather than drug therapy is often the preferred means of managing agitation in the acute phase. Medication that adversely affects cognitive function may exacerbate the problem. However, people suffering from agitation related to PTA are generally, certainly in the UK, still on acute surgical or medical wards that are least able to offer environmental interventions. On the other hand, aggression in the later stages of recovery, which may be more responsive to pharmacological treatment, tends to occur when the patient is in a rehabilitation unit, by which time environmental manipulation is more realistic.

The definition of aggression encompasses both verbal and physical aggression against self, objects and other people (Yudofsky 1986). It may also include severe irritability, violent, hostile, or assaultive behaviour and "episodic dyscontrol". A distinction is often made between instrumental and goal directed aggression and hos-

tile and/or explosive aggression (Bushman 2001). It is the latter type that is generally observed after brain injury, usually during the later stages of recovery, when the patient is no longer suffering from PTA and has regained cognitive awareness (Silver 1994). Although a distinction can be made between types of aggression there is no empirical evidence, to the authors' knowledge, that they differ in their pharmacological response.

Rationale for drug treatment of agitation and aggression

Various classes of medications have been used to treat agitation and aggression following ABI (Fugate 1997; Glenn 1991) these include:

- antipsychotics, including haloperidol;
- benzodiazepines;
- anticonvulsants particularly carbamazepine;
- buspirone (a non-benzodiazepine anxiolytic);
- antidepressants including tricyclic antidepressants (TCAs) and trazodone;
- amantadine;
- beta-blockers;
- lithium.

The rationale for the use of the various psychotropics in the management of agitation and/or aggression is poorly defined. Often medication is used to sedate the patient, rather than to treat a specific mental illness or organic brain syndrome, which may be causing the aggressive behaviour.

Antipsychotics (synonymous with major tranquillisers or neuroleptics) are commonly used to manage aggression. In the short term they may be used to quieten disturbed patients whatever the underlying psychopathology. However, the only well established long-term indication is the management of schizophrenia (Hirsch 1973).

Patients with ABI are likely to be at risk of sub-clinical epileptic activity (Schiff 1982) which has been proposed as a cause of aggression (Pincus 1991). In patients without ABI carbamazepine has been found to reduce aggression (Cowdry 1988; Foster 1989), which could be related to its anticonvulsant or mood stabilising effects.

Depression and anxiety may cause irritability and aggravate aggressive behaviour. In this case sedative antidepressants might be expected to help. Mood stabilisers, such as lithium, could also work. A further rationale for the use of antidepressants is the observation that metabolites of noradrenaline and serotonin have been found to be reduced in cerebrospinal fluid from agitated patients with ABI (van Woerkom 1977). Most antidepressants potentiate noradrenaline and/or serotonin in the brain. Lithium potentiates serotonin pathways as does buspirone, an anxiolytic.

Adverse consequences of drug treatment

There are many potential problems associated with prescribing psychotropic medication in people with ABI. Perhaps the most important is that sedating medications can cause confusion and may, therefore, exacerbate agitation occurring during the confusional state of PTA.

Patients with brain injury may be particularly vulnerable to developing neuroleptic malignant syndrome (Heird 1989; Lu 1991; Vincent 1986). Another side effect of neuroleptics is akathisia, which may increase agitation. Benzodiazepines may occasionally cause an increase in aggressive behaviour (French 1989; Gardos 1980; Gardner 1985). Recent concerns about the possible increased risk of stroke in older patients taking atypical antipsychotics also need to be considered (Herrmann 2004).

There is some evidence from human studies that anticonvulsants can have adverse effects on cognitive function when prescribed to prevent post-traumatic seizures (Dikmen 1991; Smith 1994). Furthermore, studies in animals have demonstrated the potential for neuroleptics (Feeney 1982), benzodiazepines (Schallert 1986), and anticonvulsants (Brailowsky 1986) to impair recovery from brain injury. Yet these potentially harmful drugs are being prescribed to the majority of patients admitted to hospital after head injury (Goldstein 1995).

Given the possible harmful effects of treating agitation and aggression with drugs it is important to evaluate the evidence that psychotropic drugs are effective in managing agitation and aggression following ABI.

OBJECTIVES

To determine the evidence that psychotropic medication is effective for the management of agitation and/or aggression in patients with ABI. We have also looked at evidence for unwanted side effects of medication to enable us to determine whether unwanted effects outweigh beneficial effects. All psychotropic medication was included in the review.

As there is no good evidence for a differential drug response for agitation, as opposed to aggression, this review considered any form of agitation or aggression secondary to brain injury. To enable a study of differential treatment effects, papers were classified according to the type of agitation and/or aggression and the stage of recovery.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials.

Types of participants

The review identified studies of patients suffering from acquired brain injuries that were single incidents, that is, not progressive, and were acquired in adult life. Therefore, it included anoxic brain injury, encephalitis and other forms of brain injury. Non-progressive brain injury due to alcohol or other drug abuse were also included. Cerebrovascular events (stroke) were excluded.

Agitated and/or aggressive behaviour must have been described as a presenting symptom although a formal diagnosis of organic personality syndrome with recurrent outbursts of aggression or rage (DSM-IV 1995, personality change due to a general medical condition, F07.0; aggressive type) was not required.

Agitation and/or aggression must have been measured using an explicit measurement tool that allowed a quantitative score of agitation and/or aggression.

Aggression against property or others, whether physical or verbal, was included. Aggression, which was only sexual or only against the self, was not included. Shouting behaviour that was not threatening was not included.

Age at injury greater than 10 years (to exclude patients usually classified as suffering from learning disabilities or mental impairment).

Studies in which the major problem was post-traumatic epilepsy were excluded.

There was no restriction on time between injury and treatment, severity of injury or setting of study.

Patients were classified according to the stage of recovery following the brain injury. We have attempted to distinguish agitation and/or aggression occurring earlier, during the confusional state, from aggressive behaviour occurring later. To do this we classified papers according to whether the patient was in a confused state, and/or Rancho level IV, and/or described as being in PTA, as opposed to patients who were no longer confused. In the absence of adequate information in the paper for this assignment to be made we classified papers according to cohorts less than six months and greater than six months post-injury.

Types of intervention

Any drug acting on the central nervous system (see chapter 4 of the British National Formulary):

- 4.1 hypnotics and anxiolytics;
- 4.2 drugs used in psychoses and related disorders;
- 4.3 antidepressant drugs;
- 4.4 central nervous system stimulants;
- 4.5 drugs used in the treatment of obesity;
- 4.6 drugs used in nausea and vertigo;

- 4.7 analgesics;
- 4.8 antiepileptics;
- 4.9 drugs used in parkinsonism and related disorders;
- 4.10 drugs used in substance dependence;
- 4.11 drugs for dementia;
- Other (beta-adrenoceptor blocking drugs: bupropion).

Types of outcome measures

The primary outcome measure was agitation and/or aggression. Where possible changes in the severity, frequency, or type of agitation and/or aggression were recorded.

Additional outcome measures, if available, were as follows:

- independent living
- participation in rehabilitation
- adverse events (increased cognitive impairment, side effects, death).
- health service utilisation (in particular length of stay).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Injuries Group methods used in reviews.

We searched the following electronic databases:

- Cochrane Injuries Group specialised register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- EMBASE
- National Research Register
- PsychInfo
- Psychbite
- Zetoc
- <http://www.trialscentral.org/>
- <http://www.controlledtrials.com/>
- <http://www.clinicaltrials.gov/>

Electronic searches were based on the following MEDLINE strategy, adapted as appropriate to the specifications of each database;

- #1. exp Craniocerebral-Trauma/
- #2. diffus\$ axonal injur\$.ab,ti.
- #3.((injur\$ or trauma\$ or lesion\$ or damage\$ or wound\$ or destruction\$ oedema\$ or edema\$ or fracture\$ or contusion\$

or concus\$ or commotion\$ or pressur\$) adj3 (head or crani\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemisphere or intracran\$ or orbit\$ or cerebr\$)).ab,ti.

- #4. exp Brain-Damage-Chronic/
- #5. exp Coma-Post-Head-Injury/
- #6. exp Glasgow-Coma-Scale/
- #7. exp Hematoma-Subdural-Intracranial/
- #8. exp Hematoma-Epidural-Cranial/
- #9. exp Epilepsy-Post-Traumatic/
- #10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
- #11. exp Violence/
- #12. exp Hostility/
- #13. exp Irritable-Mood/
- #14. exp Anger/
- #15. exp Impulsive-Behavior/
- #16. exp Paranoid-Behavior/
- #17. exp Antisocial-Personality-Disorder/
- #18. exp Impulse-Control-Disorders/
- #19. exp Sexual-Harassment/
- #20. exp Acting-Out/
- #21. exp Psychomotor-Agitation/
- #22. exp Self-Injurious-Behavior/
- #23. exp Juvenile-Delinquency/
- #24. exp Delirium-Dementia-Amnesic-Cognitive-Disorders/
- #25. (agitat\$ or aggress\$ or violen\$ or impuls\$ or paranoi\$ or irritabl\$ or hostil\$ or anger or angry or anti-social or impuls\$ or delinquen\$ or delirium or dement\$).ab,ti.
- #26. #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
- #27. exp central nervous system agents/
- #28. exp methotrimeprazine/
- #29. (methotrimeprazine or lamotrigine or carbamazepine or valproic acid or sertraline).ab,ti.
- #30. Triazines/tu [Therapeutic Use]
- #31. Anticonvulsants/tu [Therapeutic Use]
- #32. #27 or #28 or #29 or #30 or #31
- #33. #10 and #26 and #32
- #34. clinical trial.pt.
- #35. exp animals/
- #36. exp humans/
- #37. #35 not (#35 and #36)
- #38. #34 not #37
- #39. #33 and #38

These terms were combined with the following RCT/CCT search filter;

Highly Sensitive Search Strategy - MEDLINE (Glanville 2006)

- #1. clinical trial.pt.
- #2. randomized.ti,ab.
- #3. placebo.ti,ab.
- #4. dt.fs.
- #5. randomly.ti,ab.
- #6. trial.ti,ab.

- #7. groups.ti,ab.
- #8. #1 or #2 or #3 or #4 or #5 or #6 or #7
- #9. exp animals/
- #10. exp humans/
- #11. #9 not (#9 and #10)
- #12. #8 not #11

The journals *Brain Injury* and *Journal of Head Trauma Rehabilitation* were handsearched from the first issue through to volume 16, issue 5 (2002) and volume 17, issue 3 (2002) respectively. An update of the handsearching was done electronically using Pubmed covering the same two journals from 2002 to 2006.

A Web of Science citation index search and reference lists of relevant trials and review articles were checked for suitable trial reports.

METHODS OF THE REVIEW

The review was guided by a steering committee of Dr Keith Andrews, Dr Tom McMillan and Dr Richard Greenwood.

Trial identification and selection

One author (DLO) screened the titles, abstracts, and keywords of citations from electronic databases for eligibility. The quality of DLO's screening was assessed by a second author (SF) who read a random sample of 100 papers, for further in-depth review. A high level of concordance was achieved as only one paper was disputed, a paper which was subsequently excluded from the review.

Papers judged to be potentially eligible based on title and/or abstract were retrieved in full and these were independently assessed against the inclusion criteria by both authors.

Six papers were screened as eligible for inclusion in this review. The reference list of each paper was searched and a Web of Science Citation search conducted. Papers identified from this process were retrieved in full and were independently assessed against the inclusion criteria by both authors.

Assessment of methodological quality

The quality of the RCTs were assessed independently by both authors using a validated scale (Jadad 1996). This measure assesses the likelihood of bias in RCTs based on the adequacy of randomisation, blinding and information provided on withdrawals and dropouts. The scale grades the trial out of five with five indicating a good quality design. Disagreement on methodological quality was resolved, where necessary, by discussion.

DESCRIPTION OF STUDIES

Six randomised controlled trials were identified that met our inclusion criteria.

Four of these trials evaluated the efficacy of beta-blockers (Brooke 1992b; Greendyke 1986a; Greendyke 1986b; Greendyke 1989). Two of the trials of beta-blockers seemed to include some of the same patients (Greendyke 1986a; Greendyke 1986b). One trial evaluated the efficacy of the central nervous system stimulant, methylphenidate (Mooney 1993). One trial evaluated a drug used in parkinsonism and related disorders, amantadine (Schneider 1999).

The drugs which have been identified have been classified according to the British National Formulary categories with the exception of beta-blockers which have been collated separately under the title "other".

Studies were also classified according to the patient's stage of recovery following the brain injury. We wished to distinguish between studies of early agitation during the post-traumatic confusional state and those of later aggression in patients who were not confused. We, therefore, classified studies according to the following criteria:

- A = patients described as in a confused state, and/or Rancho level IV, and/or described as being in PTA;
- B = patients described as no longer confused, and/or out of PTA.

For a description of Rancho Los Amigos levels of cognitive functioning please refer to Growasser 1997.

In the absence of adequate information in the paper to make this assignment we classified papers according to:

- 1 = cohorts less than six months post-injury;
- 2 = cohorts greater than six months post-injury;
- 9 = not stated.

Therefore, early studies are indicated by A or 1, and late studies by B or 2.

Data from the included studies were extracted according to the headings in the included tables. A short description of each study is given in the text.

4.4 Central nervous system stimulants

Mooney 1993: methylphenidate: 2

A six-week evaluation of the effect of treatment with methylphenidate, 30 mg per day, using a randomised placebo controlled design. The 38 subjects, aged 18 to 50 years (mean age 29 years) had all suffered severe TBI with mean coma length of 17 days, mean post-traumatic amnesia of 56 days and time post-injury of more than two years (mean 27 months, SD 21 months). Nineteen subjects were allocated to each arm.

Various measures of anger were made before and at the end of six weeks' treatment.

4.9 Drugs used in parkinsonism and related disorders

Schneider 1999: amantadine: 1

This study tested the hypothesis that amantadine would decrease agitation and improve cognitive functioning in patients with TBI using a randomised, double-blind, placebo-controlled, cross-over design. The six-week trial was divided into two-week blocks of amantadine/placebo, withdrawal, placebo/amantadine. Patients were randomly allocated to one of the two treatment orders. Amantadine was gradually increased to a maximum dose of 150mg twice daily.

The 10 patients were aged 19 to 56 years (mean age 31 years) and had suffered a closed head injury. The majority had an initial Glasgow coma scale score (GCS) of below nine and all showed impairments in attention/concentration. No data were provided on the time between injury and treatment. However, the patients were described as being in an acute brain injury unit and as a large increase in orientation over the six-week trial was observed, it is likely the injury to treatment interval was less than six months.

Outcome measures consisted of the neurobehavioural rating scale (NRS) and standard neuropsychological tests of attention, orientation, memory, executive/flexibility and behaviour. These tests were administered at pre-trial and at two-week intervals.

Other (beta-adrenoceptor blocking drugs)

Brooke 1992b: propranolol: 1

This is a study of 21 subjects with severe TBI (GCS score below eight), in a combined trauma and rehabilitation centre over an 18 month period, whose main problems were agitation. The subjects were randomly assigned to a double-blind, placebo-controlled trial of propranolol, beginning with 60mg a day and increasing to a maximum of 420mg. No details were given regarding the time post-injury. The study lasted eight weeks.

Episodes of agitation were measured using the overt aggression scale (OAS) which rates the type and severity of the episode.

Greendyke 1986a : propranolol: 2

A randomised, double-blind, placebo-controlled, cross-over study of propranolol to a dose of 520mg a day (maximum recommended dose in BNF is 320mg/day). Active and placebo periods were of 11 weeks duration with a cross-over period in between (the total study period was 25 weeks). Nine patients completed the study, of whom eight had ABI (age range 27 to 75 years; mean age 51 years). The participants were 1 to 30 years post-injury. It seems very likely that seven or eight of these patients are the same as those in the Greendyke 1986b study.

Patients were rated with the nurses observational scale for inpatient evaluation (NOSIE). During the trial all regular psychotropic medication was stopped apart from paraldehyde and phenobarbital as required (the same being true for the Greendyke 1986b study).

Greendyke 1986b : pindolol: 2

This study was a randomised controlled trial of pindolol (up to 60mg per day), using a cross-over design. The treatment and placebo periods were of only two weeks. The authors appear to have used many of the same participants as an earlier study (Greendyke 1986a) looking at propranolol (see above).

The study authors give no information about the assessment scale used to rate the behaviours. They also state that the treatment order was randomly determined for each patient group rather than each individual. It is not clear what they are referring to in this statement. Ten of the 11 patients had ABI and were all described as "severely demented". The mean age range was 28 to 76 years, the mean age being 54 years.

Greendyke 1989: pindolol: 9

The first part of this study evaluated the efficacy of pindolol in managing verbal and physical aggression in 13 (10 ABI), brain-damaged male patients using a double-blind, placebo-controlled, cross-over design. In the first part of the study (21 weeks) patients were randomly allocated to either group A (pindolol) or group B (placebo). At week 10, there was a six week cross-over interval where pindolol was tapered down for group A and introduced for group B. At week 21 patients entered the second phase of the study. The objective of this phase was to determine whether pindolol would ameliorate problematic behaviours (not necessarily agitation/aggression) which were preventing the patients from being placed at a lower level of care. In this phase pindolol was re-introduced for those on the placebo and all of the patients were maintained on the drug for a further 12 weeks.

The 10 patients with ABI were aged 38 to 72 years (mean age 60.3 years). No data were given on the time between injury and treatment although the sample was described as a group of "chronically hospitalised" patients, suggesting the interval between injury and treatment was greater than six months. Entry criteria for the study required patients to be presenting with behavioural problems that prevented them being placed at a lower level of care. In phase one of the study all psychotropic medication was discontinued. Supplementary medication included phenobarbital and paraldehyde as required.

A variety of outcome measures were administered pre-trial, at cross-over and post-trial including: geriatric interpersonal evaluation scale (GIES), nurses observation scale for inpatient evaluation (NOSIE) and Sandoz Clinical Assessment-Geriatric (SCAG). Incidence of agitation and/or aggression were recorded in the nursing log and quantified using the overt aggression scale (OAS).

See 'Characteristics of included studies' table for additional information.

METHODOLOGICAL QUALITY

(* score on the Jadad 1996 scale).

Mooney 1993, methylphenidate: *1

A randomised, pre-test, post-test, control group design. Participants were randomly assigned to receive either methylphenidate or an inert placebo. The randomisation procedure was not specified. The study was single-blind with the participants being unaware of the treatment group they were in. No information was provided on withdrawals or dropouts.

Schneider 1999, amantadine: *4

A randomised double-blind, placebo-controlled, cross-over study design. Participants were randomly assigned to one of two treatment groups by the pharmacy. Group one received amantadine then the placebo after a two-week withdrawal period while group two received the placebo followed by the amantadine. The randomisation procedure was not specified. A thorough description of withdrawals and dropouts was provided.

Brooke 1992b, propranolol: *3

A randomised double-blind, placebo-controlled design. The randomisation procedure used was not specified. The drugs (active and placebo) were prepared by the pharmacy and sent under concealed allocation. The authors did not specify the number of participants who dropped out of the trial because of discharge from the unit.

Greendyke 1986a, propranolol: *4

A randomised double-blind, placebo-controlled cross-over study design. Participants were randomly allocated to receive either the active drug or placebo for 11 weeks, followed by a three week tapering period. In the final 11 weeks those in the placebo group were then given the active drug and those previously on the active drug received the placebo. The randomisation procedure was not specified. Blinding was maintained by the hospital pharmacy and remained unbroken until the trial was completed. Placebo and active drug were administered in an equal number of identically appearing capsules. One patient dropped out of the study, because he/she was unable to tolerate the placebo period.

Greendyke 1986b, pindolol: *3

A randomised double-blind, placebo-controlled cross-over study design. The treatment order was randomly determined for each patient group rather than each individual. It is not clear what the authors were referring to in this statement. Blinding was maintained by the hospital pharmacy and remained unbroken until the trial was completed. Placebo and active drug were administered in an equal number of identically appearing capsules. There was no statement on withdrawals or dropouts.

Greendyke 1989, pindolol: *4

A randomised double-blind, placebo-controlled cross-over study design. Participants were randomly assigned to one of two groups. Group A received pindolol for 10 weeks followed by the placebo for a further 10 weeks (six day tapering interval). Group B receive the placebo then pindolol. The randomisation procedure was not specified. The placebo and pindolol were powdered and adminis-

tered in capsules. Of the 15 patients recruited, 13 completed the trial: one patient was transferred to another hospital for surgery, and one patient died.

See 'Characteristics of included studies' table for additional information.

RESULTS

Because of the differences in the types of drugs used to treat agitation and aggression and the different outcome measures used in the various trials, a pooled analysis was not undertaken.

4.4 Central nervous system stimulants

Mooney 1993: methylphenidate

Mean scores and their standard errors on the anger outcome measures for the placebo group and treatment group at pre-treatment and six weeks post-treatment.

State trait anger scale (STAS)

Placebo (n = 19)

Mean = 26 (SE = 1.8)Pre test State

Mean = 29 (SE = 2.0)Post test State

Mean = 20 (SE = 2.3)Pre test Trait

Mean = 20 (SE = 1.5)Post test Trait

Treatment (n = 19)

Mean = 34 (SE = 2.5)Pre test State

Mean = 24 (SE = 1.3)Post test State

Mean = 22 (SE = 1.9)Pre test Trait

Mean = 18 (SE = 1.6)Post test Trait

(The improvement in anger scores (post-test minus pre-test) was statistically significant across the two groups.)

Source of support: not stated.

4.9 Drugs used in parkinsonism and related disorders

Schneider 1999: amantadine

No significant difference was found in any of the outcome measures between patients receiving amantadine and placebo.

No data were given for means or standard deviations.

Source of support: not stated.

Other (Beta-adrenoceptor blocking drugs)

Brooke 1992b: propranolol

The average maximum intensity of agitated episodes was significantly reduced by propranolol.

(Wilcoxin matched pairs test, $z = -2.028$, $P < 0.05$).

Data presented in Table 01 (figures taken from graphs).

Propranolol had no significant effect on reducing the average number of agitated episodes.

(Wilcoxin matched pairs test, $z = -1.5213$).

Data presented in Table 02 (figures taken from graphs).

Source of support: National Institute on Disability and Rehabilitation Research, Department of Education and Harborview Injury Prevention and Research Centre, Centers for Disease Control.

Greendyke 1986a: propranolol

The number of assaults and attempted assaults was significantly reduced by propranolol ($F = 6.50$ [1,7 df], $P < 0.05$, analysis of variance). In the seven patients who responded to propranolol, the number of assaults fell from 88 during the eleven-week placebo to 52 during the eleven-week active period.

No data were given for means or standard deviations.

Source of support: not stated.

Greendyke 1986b: pindolol

Pindolol was found to produce a significant reduction in assaultive episodes (Wilcoxon matched pairs signed ranks test $P < 0.05$).

No data were given for means or standard deviations.

Source of support: Sandoz Pharmaceuticals.

Greendyke 1989: pindolol

Pindolol had no significant effect on the incidence of agitation and/or aggression although six patients showed a decrease in overt aggression scale (OAS) scores.

No data were given for means or standard deviations.

Source of support: not stated.

DISCUSSION

This systematic review has highlighted the lack of high quality evaluations of medication for the management of agitation and/or aggression in patients with acquired brain injury (ABI). This may reflect the difficulties of carrying out research in this area. Reasons for this may be that staff are understandably not tolerant of aggression and fear entry into a trial will delay treatment, the patients are not usually in a position to give informed consent, symptoms of agitation and aggression fluctuate spontaneously, the population of patients with ABI are very heterogeneous and there are many other factors that will influence outcome apart from medication.

Nevertheless, the sensitivity of patients with ABI to adverse side effects, particularly confusion which is likely to make the agitation and/or aggression worse, means that it is important that medications are prescribed on the basis of good evidence.

Of the six studies identified, the best quality evidence, although still somewhat limited, is for beta-blockers (Brooke 1992b; Greendyke 1986a; Greendyke 1986b; Greendyke 1989). Propranolol has been found to be effective in two randomised controlled trials (RCTs); one looking at agitation in the weeks following injury and the other at aggressive behaviour months and years after injury (Brooke 1992b; Greendyke 1986a). However, these studies

used relatively small and heterogeneous samples of patients. Two of the three studies from the same research group appeared to have used largely the same cohort. Further, large doses of beta-blockers were used; many clinicians would be wary of using such large doses, particularly for treating a symptom which is not a standard indication for the drug and in a situation where the patient may not be in a position to give informed consent. However, several of the excluded studies using lower levels of evidence, lend support to the value of beta-blockers.

Methylphenidate is no longer available in the UK for routine prescription. The evidence in favour of psychostimulants is poor and must be weighed against the real risks of adverse mental side effects, particularly in a population of patients who are often vulnerable to drug abuse.

In a number of studies, the improvement seen on medication was observed within two to six weeks of starting medication. This occurred in both early and late post-injury cohorts and regardless of whether the symptom was agitation or aggression. The improvement was maintained over the treatment period, but in one RCT the placebo group also improved, though more slowly, so that by seven weeks there was no difference in agitation between the two groups (Brooke 1992b). This observation that improvements on medication occur within weeks of starting medication is consistent with clinical practice. Patients often report early gains on a new drug to treat agitation and/or aggression, but several months later, despite having remained on the medication, levels of agitation and/or aggression deteriorated to baseline levels.

There was little evidence of a differential drug effect on agitation as opposed to aggression. Beta-blockers were found to be useful for both agitation (Brooke 1992b) and aggression (Greendyke 1986a) whether occurring early or late post-injury.

Overall, the research in this area is characterised by studies using low levels of evidence. These are descriptive case reports that provide data that cannot be easily evaluated and therefore are of little value. Firstly, it is usually impossible to evaluate whether the patient did in fact respond to the medication. Secondly, even if the patients did respond, one cannot be sure that they did so at the expense of other unreported cases, who did not respond, or even got worse. Systematically collected case series at least begin to get round this second difficulty, though they are still exposed to publication bias.

In summary, this review has highlighted the need for quality research evaluating the efficacy of drugs used in the management of agitation and/or aggression in patients who have suffered an ABI. A further limitation of the work that has been published is the little attention paid to the potential for harm, and the effects of medication on the functional outcome of patients, especially in the longer term.

AUTHORS' CONCLUSIONS

Implications for practice

Numerous drugs have been tried in the management of agitation and/or aggression in acquired brain injury (ABI) but without firm evidence of their efficacy. It is therefore important to choose drugs with few side effects and to constantly monitor, in the individual, the evidence that the medication is helping.

Beta-blockers have the best evidence to support their efficacy and deserve more attention. However, if they are going to be used, it should be done with caution and preferably with the informed consent of the patient.

Carbamazepine is often the drug of choice yet hard evidence that it is effective is completely lacking. Nevertheless, in our clinical experience carbamazepine seems to be well tolerated and is generally without adverse mental/neurological side effects. Valproate may be an alternative treatment, though at present there is little evidence to support its use.

The evidence suggests that drug effects on agitation and aggression are seen early, within two to six weeks of starting medication. This would suggest that if no benefit is observed by the end of six weeks, then the drug should be tailed off and another one tried after a suitable interval.

There is no evidence that the drug response of agitation early after brain injury is different from that of later aggression. There is evidence that both respond to propranolol.

Implications for research

Better research evaluations of drugs for the management of agitation and/or aggression in ABI are required.

Given the lack of evidence for any drug or class of drugs being effective, this review suggests that RCTs are appropriate, given the current state of clinical information. Research clinicians are justified in arguing that they have no prior reason to believe that one drug treatment is better than another or that one drug treatment is better than placebo.

We would encourage the clinician to use a specific protocol with all patients, using whichever drug the individual clinician considers

appropriate. If this were done consistently on every consecutive patient then useful information would rapidly be acquired.

Case reports should not be published unless there is evidence that the authors have systematically included in their series all patients treated with the drug. More attention should be paid to N-of-1 research methods. These have the advantage of being relevant to the individual patient as well as being able to provide evidence about overall efficacy across subjects (if they are collected systematically). N-of-1 methods are particularly suitable for rehabilitation, because of the chronicity of symptoms.

Care must be taken in looking at other drug effects. Patients with aggressive behaviour are often placed on cocktails of medication. It may be the removal of a noxious drug when a new drug is started that is the therapeutic event. Or the drug under study may in fact be working by raising levels of another, active, drug already being prescribed.

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES**Characteristics of included studies**

Study	Brooke 1992b
Methods	Double-blind, randomised, placebo-controlled 8-week trial of propranolol. Treatment: n = 11. Placebo: n = 10.
Participants	21 patients. Inclusion criteria: severe, traumatic closed head-injury. LOC > 1 hour GCS < 8. Presenting with agitation.
Interventions	Propranolol (or placebo) 60mg/day increased to maximum dose of 420mg/day
Outcomes	a) Overt aggression scale (OAS) providing scores on the intensity and frequency of agitation episodes. b) Use of restraints. c) Use of supplementary medicine.
Notes	

Characteristics of included studies (Continued)

Allocation concealment A – Adequate

Study	Greendyke 1986a
Methods	Double-blind, randomised, placebo-controlled trial of propranolol using a cross-over design. 11- week block of placebo/active drug, 3-week withdrawal, 11- week block of active drug/placebo.
Participants	8 of 9 patients had ABI. Mean age 51 years, range 27-75 years. Same cohort used in Greendyke 1986b.
Interventions	Propranolol 80mg/day increased to a maximum dose of 520mg/day.
Outcomes	a) Frequency of assaultive behaviour. b) Frequency of supplementary medication. c) The Nurses observation scale for inpatient evaluation (NOSIE).
Notes	
Allocation concealment	A – Adequate

Study	Greendyke 1986b
Methods	Double-blind, randomised, placebo-controlled trial of pindolol using a cross-over design. Treatment and placebo periods = 2 weeks.
Participants	10 of 11 patients had ABI. Mean age 51.5 years, range 28-76 years. All male and presenting with aggressive and explosive behaviour secondary to brain disease or injury. All were described as 'severely demented'.
Interventions	Pindolol 10mg/day increased to a dose of 60mg/day.
Outcomes	a) Frequency of assaultive behaviour. b) Frequency of supplementary medication. c) Behavioural ratings of lethargy, hostility, uncommunicativeness, uncooperativeness and repetitive behaviour.
Notes	
Allocation concealment	A – Adequate

Study	Greendyke 1989
Methods	Double-blind, randomised placebo-controlled trial of pindolol using a cross-over design.
Participants	10 of 13 patients had ABI. Mean age 60.3 years, range 38-72 years.
Interventions	Pindolol 5mg increased to 20mg bid.
Outcomes	a) Geriatric interpersonal evaluation scale (GIES). b) Nurses observation Scale for inpatient evaluation (NOSIE). c) Sandoz clinical assessment-geriatric (SCAG). d) overt aggression Scale (OAS). e) Clinical global assessment (CGA).
Notes	Means and standard deviations were not provided for any outcome measure.
Allocation concealment	B – Unclear

Study	Mooney 1993
Methods	A randomised, pre-test, post-test, placebo-controlled, 6- week trial of methylphenidate using a single-blind design.

	Treatment: n = 19 Placebo: n = 19
Participants	38 patients with serious TBI (LOC \geq 6 hours, PTA = \geq 24 hours). Mean age 29.45 years (SD 10.02). ITI > 2 years. Exclusion: major mental disorder or LD and substance abuse in last 6 months.
Interventions	Methylphenidate increased to 30mg/day
Outcomes	a) State trait anger scale (STAS-state and trait anger). b) Katz adjustment scale (KAS-Belligerence). c) Anger-hostility score of the profile of mood states (POMS-anger hostility). d) Measures of attention and memory. e) General measures of psychological and social adjustment.
Notes	
Allocation concealment	B – Unclear

Study	Schneider 1999
Methods	Double-blind, randomised, placebo-controlled, 6-week trial of amantadine using a cross-over design.
Participants	10 patients. Mean age 31 years (range 19-56). Majority GSC < 9. Inclusion: closed head injury, no prior psychiatric history. Aged between 18-55 years, deficits in attention and/or concentration.
Interventions	Amantadine 100mg/day increased to maximum of 300mg/day.
Outcomes	a) Neurobehavioural rating scale b) Standard neuropsychological tests. Grouped into sub-tests measuring: attention, orientation, memory, executive/flexibility and behaviour. These tests were administered at pre-trial and at 2-week intervals.
Notes	Means and standard deviations were not provided for any outcome measure.
Allocation concealment	A – Adequate
LOC = Loss of consciousness ITI = Injury to treatment interval GCS = Glasgow coma scale score PTA = Post-traumatic amnesia LD = Learning disabilities	

Characteristics of excluded studies

Study	Reason for exclusion
Abraham 1990	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Single case report. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Azouvi 1999	4.8 Antiepileptics: carbamazepine. Case series study design.
Barnhill 1989	4.8 Antiepileptics: carbamazepine. Case reports. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.

Bellus 1996	4.2.3 Antimanic drugs: lithium. Case reports. Used an AB rather than an ABA design. Less than six patients were recruited.
Bouvy 1988	4.8 Antiepileptics: carbamazepine. Single case report. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Cantini 1992	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design.
Chandler 1988	4.9 Drugs used in parkinsonism and related disorders: amantadine. Case series study design. Used an AB rather than an ABA design. Less than six patients were recruited.
Chatham 1996	4.8 Antiepileptics: carbamazepine. Case series study design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Chatham 2000	4.8 Antiepileptics: valproate (Divalproex). Retrospective chart review.
Cohn 1977	4.2.3 Antimanic drugs: lithium carbonate. Single case report. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Cornier 1983	4.2.1 Antipsychotic drugs: sultopride. Single case report. Used an AB rather than an ABA design. No quantitative measure of aggression and/or agitation were used.
Duffy 1996	4.2.1 Antipsychotic drugs: clozapine. Retrospective chart review. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Elliott 1977	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Case reports. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Fann 2000	4.3 Antidepressant drugs: sertraline. Case series. Agitation and/or aggression were not the main presenting symptoms, all patients were suffering from depression. However, on sertraline, aggression (measured using the brief anger and aggression questionnaire) significantly decreased from baseline to post-treatment.
Fauman 1978	4.2.1 Antipsychotic drugs: haloperidol. Case reports. Used an AB rather than an ABA design. Less than six patients were recruited.
Geraciotti 1994	4.8 Antiepileptics: valproic acid. Single case report. Used an AB rather than an ABA design. Baseline measures were not specified and no quantitative measure of aggression and/or agitation was used.
Giakas 1990	4.8 Antiepileptics: valproate. Single case report. Used an AB rather than an ABA design. Post-traumatic epilepsy.
Glenn 1989	4.2.3 Antimanic drugs: lithium. Case series. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Greendyke 1984	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Repeated baseline single case study design. Six of the eight patients were acquired brain injury (ABI) but data was available for only four of the ABI patients. Used an AB rather than an ABA design.
Gualtieri 1991a	4.1 Hypnotics and anxiolytics: buspirone. Case reports. Used an AB rather than an ABA design.
Gualtieri 1991b	4.1 Hypnotics and anxiolytics: buspirone.

Case reports. Mild TBI case reports: aggression and/or agitation were not the presenting symptoms. Severe TBI case reports: no baseline measures were recorded before the treatment was administered and no quantitative data regarding aggression and/or agitation were presented.

Haas 1985	4.2.3 Antimanic drugs: lithium. Single case report. Baseline measures were not specified and no quantitative measure of aggression and/or agitation was used.
Hale 1982	4.2.3 Antimanic drugs: lithium. Case report. Used an AB rather than an ABA design. No quantitative measure of aggression and/or agitation was used.
Hooshmand 1974	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design.
Horne 1995	4.8 Antiepileptics: divalproex sodium. Case report. Used an AB rather than an ABA design. No quantitative measure of aggression and/or agitation was used.
Iruela 1992	4.2.1 Antipsychotic drugs: pimozide. Single case report. Used an AB rather than an ABA design.
Jackson 1985	4.3 Antidepressant drugs: amitriptyline Single case report. Used an AB rather than an ABA design.
Jackson 1989	4.3 Antidepressant drugs: amitriptyline or desipramine. Case series/RCT but no outcome data and no controlled comparison.
Kant 1998	4.3 Antidepressant drugs: sertraline. Case series. Non-blind, 8-week open trial of sertraline.
Kim 2001	4.3 Antidepressants: sertraline. Case reports. Used an AB rather than an ABA design. Less than six patients were recruited.
Kneale 1991	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design. Baseline measures were not specified and no quantitative measure of aggression and/or agitation were used.
Lee 2001	4.2.1 Antipsychotic drugs: risperidone. Case reports. Baseline measures were not specified and no quantitative measure of aggression and/or agitation were used
Levine 1988	4.1 Hypnotics and anxiolytics: buspirone. Single case report. Used an AB rather than an ABA design.
Lewin 1992	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design.
Lipper 1976	4.4 Central nervous system stimulants: dextroamphetamine Single case report. Used an AB rather than an ABA design. Also, aggression and/or agitation were not the main presenting symptoms.
Mansheim 1981	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Single case report. Used an AB rather than an ABA design.
Maryniak 2001	4.2.1 Antipsychotic drugs: methotrimeprazine. Retrospective chart review. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Mattes 1985	Other (beta-adrenoceptor blocking drugs, bupropion): metoprolol. Single case report. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
McAllister 1985	4.8 Antiepileptics: carbamazepine. One case (case 2) meets clinical criteria but fails ABA.
Meythaler 2001	4.3 Antidepressant drugs: sertraline.

	Study described as a “case series using a randomised placebo controlled cross-over design”. Agitation was not the main presenting symptom.
Meythaler 2002	4.9 Drugs used in parkinsonism and related disorders: amantadine. Study described as a “case series using a randomised placebo controlled cross-over design”. Agitation was not the main presenting symptom.
Michals 1993	4.2.1 Antipsychotic drugs: clozapine. Case series study. No quantitative data regarding aggression and/or agitation were presented. Not all patients were presenting with aggression and/or agitation as their main problem.
Morikawa 2000	4.8 Antiepileptics: carbamazepine. Single case study report. Used an AB rather than an ABA design.
Munoz 1997	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design.
Mysiw 1988	4.3 Antidepressant drugs: amitriptyline. Case series: patients maintained on amitriptyline throughout PTA or to discharge.
Nickels 1994	4.9 Drugs used in parkinsonism and related disorders: amantadine. Retrospective chart review. Used an AB rather than an ABA design. Less than six patients were recruited.
Pachet 2003	4.8 Antiepileptics: lamotrogine. Single case report. Used an AB rather than an ABA design.
Parmelee 1988	4.2.3 Antimanic drugs: lithium. Case reports. Used an AB rather than an ABA design. Less than six patients were recruited.
Patterson 1987	4.8 Antiepileptics: carbamazepine. Case series design. Less than six patients (4 = ABI, case 1, 3, 4 + 5) were recruited.
Pinaudeau 1979	4.2.1 Antipsychotic drugs: tiapride. Case series design but poorly defined. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Pinner 1988	4.3 Antidepressant drugs: trazodone. Case reports. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Pourcher 1994	4.8 Antiepileptics: carbamazepine + buspirone. Case series study design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Rao 1985	4.2.1 Antipsychotic drugs: haloperidol. Case series study design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation was used.
Ratey 1983	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Single case report. Used an AB rather than an ABA design.
Ratey 1992	4.1 Hypnotics and anxiolytics: buspirone. Single case report. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Rowland 1992	4.3 Antidepressant drugs: trazodone. Only an abstract was available as the paper was not published in full. This case series was a retrospective review of trazodone for treating post-traumatic agitation in six patients where agitated behavior scale scores and orientation group monitoring group scale scores were available.
Schiff 1982	4.2.3 Antimanic drugs: lithium. Single case report. Used an AB rather than an ABA design.
Schreier 1979	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol.

Characteristics of excluded studies (Continued)

	Single case report. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Stanislav 1994	4.1 Hypnotics and anxiolytics: buspirone. Case reports. No quantitative data regarding aggression and/or agitation were presented.
Stanislav 2000	4.2.1 Antipsychotic drugs: droperidol. Controlled group comparison of intramuscular droperidol with other agents administered intramuscularly to manage agitation.
Stewart 1985	4.8 Antiepileptics: carbamazepine. Single case report. Used an AB rather than an ABA design.
Szlabowicz 1990	4.3 Antidepressant drugs: amitriptyline Single case report using an ABA design. However, no quantitative measure of aggression and/or agitation was used.
Teng 2001	Other (beta-adrenoceptor blocking drugs, bupropion): bupropion. Single case report. Used an AB rather than an ABA design.
Wolf 2001	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol + leuprolide. Case report. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Wroblewski 1997	4.8 Antiepileptics: valproic acid. Case reports. Used an AB rather than an ABA design. Less than six patients were recruited.
Yudofsky 1981	Other (beta-adrenoceptor blocking drugs, bupropion): propranolol. Single case reports. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.
Zimnitzky 1996	4.2.1 Antipsychotic drugs: risperidone. Single case reports. Used an AB rather than an ABA design. Baseline measures were not taken before the intervention was administered and no quantitative measure of aggression and/or agitation were used.

Please refer to the additional tables for further information.

Characteristics of ongoing studies

Study	Warden 2000
Trial name or title	A randomized placebo-controlled trial of sertraline for the neurobehavioral sequelae of traumatic brain injury
Participants	Patients will be active duty or other military beneficiaries, between 18 and 65 years of age, with traumatic brain injury (within six months of injury). Males and non-pregnant females may participate.
Interventions	Sertraline.
Outcomes	Irritability, depression, frustration, anxiety and other post-concussive symptoms.
Starting date	Study start: February 2000; Expected completion: February 2010 Last follow-up: February 2005; Data entry closure: February 2010
Contact information	Deborah L Warden, MD deborah.warden@amedd.army.mil
Notes	

ADDITIONAL TABLES

Table 01. Brookes 1992b (average maximum intensity of agitated episodes)

	Placebo	Active drug	Dose (mg)
Baseline	0.45	1.35	0
Week 1	3.55	4.35	60
Week 2	4.75	3.55	180
Week 3	4.5	3	300
Week 4	4.5	2.3	420
Week 5	3.50	0.63	420
Week 6	4	1.2	120
Week 7	1.25	1	0

Table 02. Brookes 1992b (average number of agitated episodes)

	Placebo	Active drug	Dose (mg)
Baseline	4	3.3	0
Week 1	8	9.5	60
Week 2	9.3	8	180
Week 3	7.5	4	300
Week 4	6.7	4.5	420
Week 5	3.5	1.8	420
Week 6	4	2.5	120
Week 7	2.3	2.4	0

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [*therapeutic use]; *Aggression; Amantadine [therapeutic use]; Anxiety [*drug therapy]; Brain Injuries [*psychology]; Methylphenidate [therapeutic use]; Neuroprotective Agents [*therapeutic use]; Pindolol [therapeutic use]; Propranolol [therapeutic use]; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title Pharmacological management for agitation and aggression in people with acquired brain injury

Authors	Fleminger S, Greenwood RJ, Oliver DL
Contribution of author(s)	SF updated the review (July 2006). RG and SF designed the protocol and wrote the research proposal for application for funding. RG commented on the protocol and review. SF was involved in the designing and running of the search strategy, screened titles and abstracts for eligibility, extracted data, critically evaluated and quality assessed the included studies and wrote up the review. SF supervised the work of research assistant, DLO. DLO assisted in the writing of the protocol and in the designing of the search strategy. Advice on the search strategy was provided by Martin Hewitt, information specialist, King's College. DLO screened titles and abstracts for eligibility, obtained references, contacted authors for further information, extracted data, quality assessed the included studies and assisted in the writing of the review.
Issue protocol first published	2001/4
Review first published	2003/1
Date of most recent amendment	22 August 2006
Date of most recent SUBSTANTIVE amendment	22 August 2006
What's New	The searches were updated in June 2006, no new studies for inclusion were found, however, one ongoing study has been identified (Warden 2000). The review text has been revised and updated.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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