Case Study 3

55 year old male, inebriated, fell down stairs, very agitated.

3.1 Problem List

Q1. Create a problem list

3.2 Non-Pharmacological Treatment of Agitated and Disruptive Behavior

3.2.1 Assessment of Agitation and Aggressive Behavior

Q2. What test is available to assess for agitated and aggressive behavior? What are its strengths and limitations?
Q3. What are some of the practical advantages of using an objective scale for assessing agitation?

3.2.2 Treatment of Agitation and Aggression

3.2.2.1 Non-Pharmacological Methods

Q4. What non-pharmacological methods of managing agitation and aggressive behavior are available in a case such as this?
Q5. Which non-pharmacological options are available to treat his agitation and disruptive behavior which have been studied in research studies?
Q6. What evidence is there for antecedent management and/or feedback?
Q7. What evidence is there for multi-intervention training programs?
Q8. What is the evidence for music therapy for agitation?
Q9. Two non-pharmacological methods of managing agitation and aggressive behavior which have been studied in the literature include the 1) Stimulus control learning procedure and 2) Response consequence learning. Describe these two approaches.

3.3 Pharmacological Treatment of Agitated and Disruptive Behavior

3.3.1 Principles of Pharmacological Management

Q10. What are some principles for using pharmacological measures in the treatment of aggressive and agitated behaviour?

3.3.2 Recommended Pharmacological Measures

Q11. When non-pharmacological measures are unsuccessful which medications are recommended to decrease aggressive and agitated behaviours?

3.3.3 Evidence for Pharmacological Measures Used to Treat Aggressive Behaviours Post TBI

Q12. What is the evidence for medications used to decrease aggressive behaviours post TBI?

3.3.4 Individual Pharmacological Agents

3.3.4.1 Atypical Antipsychotics

Q13. Comment on the use of Atypical antipsychotic medications in the treatment of agitated and aggressive behaviour?

3.3.4.2 Valproic Acid and Divalproex

Q14. What type of medication is Valproic Acid; what are its advantages?
Q15. What is the evidence supporting the efficacy of valproic acid for aggressive behavior post ABI?

3.3.4.3 Carbamazepine (Tegretol)

Q16. What type of medication is carbamazepine?
Q17. What evidence is there that carbamazepine is effective in treating behavioral issues post ABI?

3.3.4.4 Beta-Blockers

Q18. What beta-blockers are used to treat aggression and why?
Q19. How do Beta-blockers work to treat aggression following ABI?
Q20. What is the evidence for Beta-blockers in the management of aggression post ABI?

3.3.4.5 Methylphenidate

Q21. What is the evidence supporting the efficacy of methylphenidate for aggressive behavior post ABI?

3.3.4.6 Selective Serotonin Reuptake Inhibitor

Q22. What type of medication is sertraline and how does it work to control aggression post ABI
Q23. What is the evidence for Sertraline in the management of aggression post ABI?

3.3.4.7 Tricyclic Antidepressants

Q24. What is the evidence for the use of Amitriptyline in the management of agitation and aggressive behavior?

3.3.4.8 Trazodone

Q25. What is the evidence for the use of Trazodone in the management of agitation and aggressive behavior?

3.3.4.9 Amantadine

Q26. What type of medication is amandatine?
Q27. What evidence is there that amantadine is effective in treating behavioral issues post ABI?

3.3.4.10 Methotrimeprazine (Nozinan)

Q28. What type of medication is methotrimeprazine?
Q29. What evidence is there that methotrimeprazine is effective in treating behavioral issues post ABI?

3.3.4.11 Lithium Carbonate

Q30. What evidence is there that lithium carbonate is effective in treating aggressive behavior?

3.3.4.12 Haloperidol

Q31. What evidence is there that haloperidol is effective in treating aggressive behavior?

3.4 Sleep Disturbance

Q.32 What medications would be recommended to help him sleep?

Case Study 3

Case Study

A 53-year old male fell down the stairs while intoxicated. He had a history of chronic alcoholism, low back pain, poor relationship history, poor social supports, and was unemployed at the time of the accident. His injuries included: a basal skull fracture and left fronto-temporo-parietal SDH (drain via burr hole, bifrontal hemorrhagic ICH). He was admitted to rehabilitation 7 days post- injury.

The patient was ambulatory, although he had been seen to stagger occasionally, and was somewhat neglectful on the right side. His speech was intelligible, though slurred and loud, at times sounding intoxicated. He made inappropriate comments to staff, particularly sexually inappropriate remarks. When agitated he tended to swear loudly and gesture aggressively (waved his fist around). He is perseverative regarding a number of things: Making phone calls, leaving the unit, going for a smoke, going home, and people stealing his belongings, etc.

He had an attendant to follow him, but the attendant avoided engaging him, as he has hit staff previously. He could not be restrained in a wheelchair, as he would stand tied in the wheelchair, or would tip the chair. He could not be restrained in bed as he attempted to escape. He would become entangled, agitated, and kick staff as they were attempting to apply the restraint. He lacked insight into his behavior and did not understand why staff were "keeping him locked up in this jail".

Other staff, patients, and families were afraid of him and tried to avoid him. Other brain injured patients were aroused by him and became violent and aggressive due to his behaviour. He frequently refused all of his medications; therefore, he was not consistently on any pharmacological agents to manage his agitation.

3.1 Problem List

Q1. Create a problem list:

Answers

- Intoxicated
- Basal skull fracture
- Left fronto-temporo-parietal SDH (drain via burr hole, bifrontal hemorrhagic ICH
- Speech (Sounded intoxicated)
- Agitated, sexually inappropriate
- Perseverative on multiple things
- Not safe to be restrained
- Lacks insight into his behaviour and deficits
- Violent/aggressive
- Refuses all of his medications

3.2 Non-Pharmacological Management of Agitation and Disruptive Behaviour

3.2.1 Assessment of Agitation and Aggressive Behaviour

Q2. What test is available to assess for agitated and aggressive behavior? What are its strengths and limitations?

Answer
Agitated Behavior Scale, designed to assess agitation in patients by those working with them. 14 item scale, with each item scoring 1-4 (total range 14-56).

Strengths
The length of the scale (14 questions), amount of time to complete it (<30 minutes) and its availability makes the scale very practical.

Weaknesses
Risk of over diagnosis of agitation (Corrigan & Mysiw, 1988).

Discussion
To measure agitation post-injury, the Agitated Behavior Scale was developed (Bogner & Corrigan, 1995). The ABS was designed to assess agitation in patients by those working with them. According to Levi et al.(2005), despite the availability of the scale, agitation remains unmeasured by most who work with the TBI population. The scale, which began as a 39 item scale, was reduced to 14 items, with each item scoring 1 to 4 (from absent to present to an extreme degree). The scale, which was originally tested by nurses, occupational therapists (OT), physiotherapists (PT) and other hospital staff, was designed to be used by allied health professionals (Corrigan, 1989).

Q3. What are some of the practical advantages of using an objective scale for assessing agitation?

Answers
1. Assess pattern of agitation
2. Assess the level of agitation, which then can dictate treatment
3. Assess the response of agitation to interventions
4. Numbers mean something; ABS >21 = agitation, <23 unlikely to be violent, >28 = treatment with pharmacological agents

3.2.2 Treatment of Agitation and Aggression Post-TBI

Case Study (Continued)

The patient does not want to take medications but is still exhibiting aggressive and agitated behaviour.

3.2.2.1 Non-Pharmacological Methods

Q4. What non-pharmacological methods of managing agitation and aggressive behavior are available in a case such as this?

Answer

- Do not leave patient alone
- Keep noise and traffic in room to a minimum
- Familiarize with basic information
- Physical reassurance through talking or touching patient
- Accommodation in a highly-structured setting
- Establish desired behaviour
- Remove patient from group or change activity if agitation increases
- Freedom of movement to control outbursts
- Stimulating simple self-care tasks and participation
- Assess for treatable pathology
- Assess for sleep/wake cycle

Q5. Which non-pharmacological options are available to treat his agitation and disruptive behavior which have been studied in research studies?

Answers

1. Feedback
2. Cognitive training
3. Music therapy

Discussion

According to Leon-Carrion & Dominguez-Morales (2006), emotional problems in 70% of patients improved after an intensive, holistic, and multidisciplinary program. The interdisciplinary holistic program consists of a team of neuropsychologists, speech therapists, neurologists, psychiatrists, and physical therapists etc. Agitation and aggression can be exacerbated by drug or alcohol abuse, alcohol, intoxication, and craving/withdrawal syndrome. Psychiatric assessment for evidence of mental illness and consent to treatment is often necessary.

Q6. What evidence is there for antecedent management and/or feedback?

Answer

1. There is Level 4 evidence that Antecedent management, and/or feedback of consequences can reduce aggression and/or agitation

Discussion

Due to the individual's needs and physical or emotional disabilities following an ABI, it is extremely difficult to assess behavioural management programs overall, as they are designed for a specific person with a specific issue or issues. Studies that have been reviewed as part of the evidence based review of acquired brain injury (ERABI) and challenging behaviours (Rees et al., 2008) include those that looked at the benefits of token economies, positive reinforcements, anger management, and social skills training. Each of these techniques alone or in combination has been used to help reduce the level of agitation or aggression someone with an ABI may be experiencing.

Overall, 9 studies looked at the benefits of antecedent controls or the feedback of consequences in reducing undesirable behaviour. Although the sample sizes in each study were small, there is **some** evidence to suggest that a behavioural approach is successful in reducing undesirable behaviour (Rees et al., 2008).

Interventions aimed at reducing the amount of aggressive behaviour seen following an ABI were shown to be effective. Again, the number of subjects in the various studies (n=6) ranged from 2 to 37.

Table 1: Summary of Therapies Used to Improve Behaviour

Conclusions	Levels of Evidence
Natural setting behavior management may help to change behaviour.	Level 2
Participating in a Coping Skills Group assisted in improving adaptive coping in the long term.	Level 2
Anger management reduces aggressive behaviour according on one RCT.	Level 2
Social skills training reduces aggressive behaviour.	Level 4

For a more detailed discussion the various studies please see Rees et al., (2008)

A sampling of the research is shown below:

Feeney & Ylvisaker (1995) in a study of only 3 late adolescent males with a MVA-induced traumatic brain injury, showed that by structuring the environment initially with high support, and then reducing it, and involving the clients in a collaborative manner, aggressive behaviour was significantly reduced.

Schlund & Pace (1999) evaluated the impact of systematic databased feedback on 3 TBI patients with maladaptive behaviour. Maladaptive behaviours consisted of pseudoseizures, non-compliance with rules, verbal aggression, and sexually inappropriate behaviour. Variability and frequency of maladaptive behaviour generally decreased from baseline (2 to 5.1 per week) to completion (0.18 to 1.8 per week).

Burke et al. (1988) found that the positive reinforcement significantly and dramatically reduced aggressive behavior in 5 subjects with closed head injuries.

Eames & Wood (1985) conducted a study with 24 severely injured ABI subjects (mean LOC 7.8 +/- 6 weeks) whose disturbed behaviours prevented rehabilitation in ordinary settings. Patients were placed in a specialized TBI unit which used a wide range of

physical, cognitive behavioural, occupational, and social techniques based on positive reinforcement and a token economy. They examined the effects of treatment from discharge to follow up (mean follow-up 19 months). More than 2/3 of patients had improved placements after treatment; only one person had a substantial improvement. Fewer than 1/3 made no change, and no one was worse placed. Quality of life improved, as measured by improved relationships with caregivers and an improvement in living arrangements.

Q7. What evidence is there for multi-intervention training programs.

Answers

1. There is Level 2 evidence that Natural Setting Behavior Management may help to change behavior.
2. There is Level 2 evidence to suggest that participating in Coping Skills Group assisted in improving adaptive coping in the long term.
3. There is Level 2 evidence, based on one RCT, that anger management reduces aggressive behavior.
4. There is Level 4 evidence that social skills training reduce aggressive behaviour.

Discussion

Multi-interventional Training Programs include:

- Social Skills Treatment
- Natural Setting Behavior Management
- Participating in a Coping Skills Group
- Anger Management

Structuring an individual's environment initially with high support, and then reducing it, and involving the clients in a collaborative manner, aggressive behaviour was significantly reduced (Feeney & Ylvisaker, 1995)***.*** The impact of systematic databased feedback *was* evaluated on 3 TBI patients with maladaptive behaviour (pseudoseizures, non-compliance with rules, verbal aggression and sexually inappropriate behavior). Variability and frequency of maladaptive behaviour generally *decreased* from baseline (2 to 5.1 per week) to completion (0.18 to 1.8 per week) Schlund & Pace, 1999).Positive reinforcement significantly and dramatically was found to reduce aggressive behavior in patients with closed head injuries Burke et al., 1988). ABI patients whose disturbed behaviours prevented rehabilitation in ordinary settings were placed in a specialized TBI unit that used a wide range of physical, cognitive behavioural, occupational and social techniques based on positive reinforcement and a token economy. Post treatment 2/3 of patients had improved placements after treatment; only one person had a substantial improvement. Quality of life had improved as measured by improved relationships with caregivers and an improvement in living arrangements (Eames & Wood, 1985)***.***

Social Skills Treatment

McDonald et al. (2008) found individuals who had been randomly assigned to a social skills training group (where they received both group and individual sessions) social behavior improved; however, when looking at the treatment effects results indicate no

interaction effects for the social group relative to the control or waitlist groups. Those in the skills training group made significant improvement on the Partner Directed Behaviour Scale (PDBS) compared to the placebo group and the waitlist group. Changes were not noted for any group when looking at social functioning and social participation post treatment. Treatment effects were found to be modest at best and limited to direct measures of social behaviour. In an earlier study individuals participated in asocial skills training program lasting approximately 28 weeks. Behaviours receiving the lowest ratings were targeted for intervention. The program was shown to be successful in remediating a variety of social deficits found in the study participants. The interventions were particularly effective when addressing motoric target behaviours rather than complex verbal behaviours (Brotherton et al., 1988).

Natural Setting Behaviour Management

In a RCT conducted by, Carnevale and colleagues (2006), individuals were randomly placed in one of three groups (the control group (no treatment was given), the education group and the Natural Setting Behaviour Management group (who received both education and participated in an individual behavior modification program).Changes in behavior were not seen at the first two follow-up time periods; however, differences were found between the control and the experimental groups in the motion exhaustion scale. Treatment did not affect the scores on the neurobehavioural functioning inventory.

Coping Skills Intervention

Although not stable over time, both groups increase their adaptive coping skills following their participation in the coping skills group (CSG). However, no significant changes in their anxiety or self-esteem scores following the CSG. Results also showed that levels of depression and psychosocial dysfunction improved for both groups, suggesting participation in the CSG did not affect their scores (Anson & Ponsford, 2006).

Anger Management

In one cohort study, O'Leary (2000) had participants attend weekly sessions for 10 weeks. Sessions addressed coping skills and managing daily stress. Results showed that aggression decreased following these weekly session and these effects were maintained for another 10 weeks. Medd & Tate (2000) evaluated the effectiveness of an anger management therapy program in 16 ABI patients. Results indicated a decrease in anger (as measured by the State-Trait Anger Expression Inventory) immediately and two months following treatment.

Q8. What is the evidence for music therapy for agitation?

Answers

1. There is Level 2 evidence based on a non-RCT that music therapy reduces agitation.
2. There is Level 4 evidence that music therapy reduces psychomotor agitation
3. There is Level 4 evidence to suggest that music therapy improves mood.

Discussion
Music therapy is an approach that *"consists of using music therapeutically to address physical, psychological, cognitive and/or social functioning for patients of all ages"* (American Music Therapy Association, 2004). Music therapy has been used with a variety of patients and was formally recognized as a therapeutic tool in 1950. Later music therapy has been used with TBI patients to decrease agitation.

Formisano et al. (2001) conducted one study and found that music therapy had a beneficial effect in reducing post-coma agitation. Baker (2001)showed that agitation decreased significantly after exposure to the live and taped music ($p<0.001$). According to Baker et al. (2005), in which 4 subjects participated in 15 individual music therapy, there were differences between subjects on their responses to all 8 of the mood scales.

Q9. Two non-pharmacological methods of managing agitation and aggressive behavior which have been studied in the literature include the 1) Stimulus control learning procedure and 2) Response consequence learning. Describe these two approaches.

Answer
Stimulus control learning procedure
1. Attempts to change behavior by manipulating antecedent events – relies on the patient's ability to discriminate those aspects of the environment that act as cues for an undesirable behavior.

Response consequence learning
1. Focuses on the association between the behavior and its subsequent consequences, i.e time out.

Discussion
"A systematic evaluation of the coma-emerging patient is the obvious first step for the optimal treatment of secondary behavioral disorders. Ideally, the target behaviors of posttraumatic agitation should be divided into those that are most amenable to nonpharmacologic intervention versus those that require or optimally respond to psychopharmacologic intervention…" (Mysiw & Sandel, 1997). Although unproven, it is logical to assume that the most effective intervention for posttraumatic agitation would combine both pharmacologic and nonpharmacologic strategies.

Behavioral Intervention
"Two broad types of behavioral techniques have been effective in the management of TBI survivors: response-consequence learning and stimulus-control learning (Wood, 1990).

The stimulus-control learning procedure *attempts to change behavior by manipulating antecedent events. This technique relies on the patient's ability to discriminate those aspects of the environment that act as cues for an undesirable behavior. Therefore, the patient is asked to recognize and respond to those signals with more socially appropriate behaviors.* ***Response-consequence learning*** *focuses on the association between the behavior and its subsequent consequences. An example of response-consequence technique is the time-out method. A token economy is yet*

another example of response-consequence learning. This involves identifying target behaviors to be increased and constructing contingencies that specify the number of tokens received for each target behavior (Corrigan et al., 1993).

Both response-consequence learning and stimulus-control techniques are dependent on associational learning. For the coma-emerging patient with significant posttraumatic agitation, this type of learning is frequently, profoundly impaired. Under these circumstances, a structured milieu that is consistent, provides an assortment of productive activities, and minimizes excessive sensory stimulation, is the more commonly utilized, non-pharmacologic, behavioral intervention (Corrigan et al., 1993).

The acutely agitated brain injury survivor occasionally responds to de-escalation techniques, but verbal de-escalation of aggression is rarely effective with psychotic or organic brain syndrome patients (Tardiff, 1992). Restraints or seclusion represent controversial forms of emergent, nonpharmacologic interventions for acutely violent, agitated survivors. Both of these techniques warrant close supervision by nursing staff and frequent evaluations by the medical staff. Institutional guidelines typically outline indications for restraints or seclusion, supervision requirements, and mandates that authorizing orders are time limited. Additionally, these guidelines typically mandate that orders for a restraint or seclusion must be reviewed and renewed periodically (Tardiff, 1992).

3.3 Pharmacological Management of Agitation and Disruptive Behaviour

Case Study (Continued)

The patient continued to exhibit aggressive and agitated behaviour. His Agitated Behaviour Scale score was 32. The staff pushing for pharmacological treatment of his aggressive and agitated behaviour.

3.3.1 Principles of Pharmacological Management

Q10. What are some principles for using pharmacological measures in the treatment of aggressive and agitated behaviour?

Answers

1. Pharmacological agents should only be used as a last resort (ABS > 28).
2. Careful considerations of the sensitivity of people with TBI to psychotropic medications which should be used with caution.
3. With medications “start low and go slow” and titrate to an optimal dose; but get to a therapeutic dosing before abandoning use.
4. Develop clear cut goals and metrics to assist in determining when to stop treatment (i.e. consider weaning off medication when ABS < 21).
5. Be alert to side effects and undesired effects.
6. Minimize use of Benzodiazepines and neuroleptic antipsychotic medications such as Haldol as animal studies suggest these medications may slow brain recovery.

3.3.2 Recommended Pharmacological Measures

Q11. When non-pharmacological measures are unsuccessful which medications are recommended to decrease aggressive and agitated behaviours?

Answers

Initially
Atypical antipsychotics prn – risperidone up to 3 gm daily; alternative seroquel or olanzapine

Later *(if ABS ≥ 28 then provide scheduled dose medications*
1. Beta-blockers
2. Anticonvulsants (i.e Valproic Acid)
3. SSRI (Sertraline)
4. Tricyclic antidepressants (Amtriptyline titrated up to 75 mg/day)
5. Methylphenidate
6. Avoid the use of antipsychotic drugs such as Haldol

Discussion
According to the ERABI (2008):
The use of multiple neuropharmacological agents early in the treatment of posttraumatic brain injury agitation may be an effective therapeutic intervention for both behavioral and cognitive problems. The best evidence of effectiveness in the management of agitation and/or aggression following ABI was for beta-blockers (Fleminger et al., 2006). Anticonvulsants and beta-blockers are the two classes of drugs most often recommended. More research is needed to assess the role of other medications and medication combinations such as amantidine, ritalin, trazodone and dexedrine (Rosati, 2002).

According to ABIKUS Guidelines (2007)

1. *"There should be careful considerations of the sensitivity of people with traumatic brain injury to psychotropic medication before trial use. Psychotropic medications should be used with caution. Where medications are clinically indicated 'start low and go slow', keep under direct clinical monitoring to ensure that the drug is tolerated and producing the expected improvement and used with caution where indicated. (pg 18)*

2. *Perform a detailed physical exam prior to commencing any trial of medications. People with traumatic brain injury and their caregiver should be asked about any prescribed medications, over the counter remedies, herbs or supplements they are taking to check for potential interactions and adverse effects. (pg 18)*

3. *Appropriate investigations should be completed prior to medication trials to rule out and minimize metabolic abnormalities including evaluation of: plasma blood sugar, electrolytes, hormones, hemoglobin, oxygenation and infection. (pg 18)*

4. *Clinicians should also consider the possibility of brain injury related sleep disorders as a cause of cognitive and other behavioural changes. (pg 18)*

5. *Any trial of medication for a person with traumatic brain injury should be preceded by a clear explanation to the person with traumatic brain injury and their caregivers, and a caution that effects of medications are less predictable in people with traumatic brain injury. (pg 18)*

6. *Minimize use of benzodiazepines and neuroleptic antipsychotic medications as animal studies suggest these medications may slow recovery after brain injury. (pg 18)*

7. *Beta Blockers are recommended; a guideline for the treatment of aggression after TBI. Studies reported the efficacy of both propranolol (maximum dose 420-520 mg/day) and pindolol (maximum dose 40-100 mg/day) in the treatment of aggression in this population. (pg 19)*

8. *Anticonvulsants: Carbamazepine and/or Valproic Acid may be used to decrease the incidence of aggressive behaviours. (pg 19)*

9. *Valproic Acid may be preferred over phenytoin post brain injury as it does not have any significant neuropsychological side effects, and is effective for controlling established seizures and stabilizing mood. (pg 19)"*

3.3.3 Evidence for Pharmacological Measures Used to Treat Aggressive Behaviors Post TBI

Q12. What is the evidence for medications used to decrease aggressive behaviors post TBI

Answer:

Medications to Decrease Aggressive Behavior Post TBI (ERABI 2008)

Medication	Recommended doses	Level of evidence	Recommendations
Divalproex		Level 4	Reduce a variety of neurobehavioural symptoms including ABI-induced agitation
Carbamazepine	400 mg -800 mg per day for 8 weeks	Level 4	Reduced agitation
Lamotrigine	25 mg daily	Level 5	Reduced aggressive behaviour
Pindolol	60 mg -100mg/day	Level 1	Reduced aggressive behaviour
Propranolol	520 mg/day 60 mg -420 mg/day	Level 1	Reduced agitation

Methotrimeprazine	2-50 mg. 2-4 times per day	Level 4	Reduced agitation
Droperidol	2.5-5 mg IM	Level 4	Reduced agitation
Haloperidol	1-6 mg	Level 4	Reduced agitation
Quetiapine	25 to 300mg	Level 4	Reduced aggression
Sertraline HCH	50 mg- 200 mg per day	Level 4	May reduce aggressive behaviour
Amantadine		Level 4	For early treatment of post-TBI agitation
Trazodone		Level 4	For early treatment of post-ABI agitation
Lithium carbonate		Level 5	Reduce agitation

The ABIKUS (2007a) was a consensus driven document; the ERABI (Rees et al., 2008) dealt with the published research. A comparison of the two is shown below:

ABIKUS (2007) and ERABI (2008) Comparison		
Medications	**ABIKUS**	**ERABI**
Valproic Acid and Divalproex	Recommended	Level 4 evidence for Divalproex
Methylphenidate	Recommended	No evidence
SSRIs	Recommended	No evidence
Beta-blockers	Recommended	No evidence
Tricyclic antidepressants	Recommended	Level 4 evidence for Trazodone
Amantadine	No comment	Evidence is uncertain
Methotrimeprazine	No comment	Level 4 evidence
Other Anticonvulsants	No comment	Level 4 evidence for Carbamazepine
Lithium carbonate	No comment	Level 4 evidence

3.3.4 Individual Pharmacological Agents

3.3.4.1 Atypical Antipsychotics

Q13. Comment on the use of atypical antipsychotic medications in the treatment of agitated and aggressive behaviour?

Answers

1. Atypical antipsychotic medications include risperidone, seroquel and olanzapine
2. Generally used early on because of their relatively rapid action.
3. Always concern about the use of neuroleptic medications, particularly given it potential impact on neurological recovery.

Discussion

Atypical antipsychotic drugs such as olanzapine and risperidone are increasingly being used as first line treatment for individuals with psychotic disorders and increasingly being used for decreasing agitation and aggression. According to Warden (2006), studies were conducted which reported that these drugs can be effective for some patients with traumatic brain injury. It has been recommended that one start with dose of olanzapine

2.5-5 mg QHS or BID and then increase in increments of 2.5-5 mg up to 20 mg/day. Risperidone would start with 0.5 mg QHS or BID and increase in increments of 0.5-1mg up to 4-6 mg/day (Silver & Arciniegas, 2007), although many clinicians will stop at 3 gm/day.

3.3.4.2 Valproic Acid and Divalproex

Q14. What type of medication is Valproic Acid and what are its advantages?

Answers

1. Valproic acid is, primarily, an anticonvulsant drug.
2. Divalproex sodium is a variant of valproic acid.
3. Inhibits GABA catabolism and potentiates its postsynaptic effect.
4. Has one of the best adverse neuropsychological side-effect profiles.
5. Effective for both seizures and aggressive behaviour (Dikmen et al., 2000; Wroblewski et al., 1997)
6. Effective for a number of psychiatric disorders including bipolar disorder.

Q15. What is the evidence supporting the efficacy of valproic acid for aggressive behavior post ABI?

Answers

1. Based on a single RCT, there is Level 1 evidence that valproic acid does not have any significant neuropsychological side effects, does not prevent post-traumatic seizures, but is effective for controlling established seizures and stabilizing mood.
2. Based on the findings from 2 studies, there is Level 4 evidence that valproic acid and divalproex are effective for reducing a variety of neurobehavioral symptoms including destructive and aggressive behaviours.
3. Overall, Valproate does not appear to have significant neuropsychological side effects, but does appear to stabilize mood and irritability, and control seizures.

Discussion

Dikman et al. (2000) conducted a double-blind RCT examining the efficacy of valproic acid in post-traumatic seizure prevention with assessment of neuropsychological side effects. The authors concluded that valproate did not have any significant neuropsychological side effects and was effective for controlling established seizures and stabilizing mood. However, it did not prevent the onset of post-traumatic seizures.

The effectiveness of valproic acid was investigated for improving destructive and aggressive behaviours. It was found to be extremely effective in reducing and improving these negative behaviours (Wroblewski et al., 1997). Kim & Humaran (2002) carried out a retrospective chart review on 11 patients with ABI referred for psychiatric treatment. They evaluated the effects of divalproex on reducing a variety of neurobehavioral symptoms including aggression, impulsivity, psychosis, mania, anxiety, hypomania, and irritability. They found that it was effective, as measured by the Clinical Global Impression Scale (a subjective psychiatric rating scale). Similarly, Chatham Showalter &

Kimmel (2000) retrospectively found a significant reduction in symptoms of agitation in 29 patients.

The starting dose of valproic acid may range from 125 to 1000 mg.day. Valproic acid has a very favourable side effect profile, especially for cognitive side effects. Potential side effects of the medication include gastrointestinal distress, headaches, dizziness, thrombocytopenia, hepatitis, and pancreatitis (rare).

3.3.3.3 Carbamazepine (Tegretol)

Q16. What type of medication is carbamazepine?

Answers

1. Carbamazepine inhibits voltage-dependent neuronal sodium channels (Schachter, 1997). As indicated in the CPS, carbamazepine blocks the physiological action of acetylcholine and has a moderate anticholinergic action that is responsible for some of its side effects (2008).
2. It has been shown to successfully treat various seizure disorders and obsessive compulsive disorder.
3. It has been suggested that carbamazepine may be effective in treating aggressive behaviour post TBI.

Q17. What evidence is there that carbamazepine is effective in treating behavioral issues post ABI?

Answer

1. There is very limited evidence that carbamazepine is effective in treating behavioural issues post ABI.

Discussion

It is believed that carbamazepine may be an effective alternative to lithium (Azouvi et al., 1999b). Azouvi showed that agitation and behaviour initially improved with carbamazepine but that improvement was much less significant over time.

3.3.3.4 Beta-Blockers

Q18. What beta-blockers are used to treat aggression and why?

Answer

1. Propanolol and Pindol are the two beta-blockers used because they both cross the blood-brain barrier.

Q19. How do Beta-blockers work to treat aggression following ABI?

Answer

1. Beta-blockers work to improve agitation, anxiety, aggressive behaviour, and restlessness, likely through reduction of sympathetic activity.

Discussion

It has been suggested that beta-blockers may improve agitation, anxiety, and aggressive symptoms following brain injury, as well as to reduce restlessness. Often, dosage is high, leaving patients vulnerable to such adverse effects as sedation, depression, and lethargy, although it does not seem to negatively affect motor recovery post-injury (Levy et al., 2005; Levy et al., 2005).

Pindolol is a beta- blocker unlike many others; it exerts a partial agonist effect, providing a slight stimulation of the blocked receptor and maintaining a better resting sympathetic tone. Propranolol is a non-selective beta-blocker, used for the reduction of aggressive behaviours associated with compromised brain function. It is not known how this drug works to affect behaviour; however, it appears to lack the serious cognitive and affective side effects of other medications or physical restraints used to treat agitation post-injury (Levy et al. 2005)

Q20. What is the evidence for Beta-blockers in the management of aggression post ABI?

Answer

1. There is Level 1 evidence that pindolol and propanolol improves aggression following brain injury.
2. Overall, beta-blockers improve aggressive behaviour following brain injury.

Discussion

Greendyke & Kanter (1986) investigated the effectiveness of the beta-blocker, pindolol, for the improvement of behaviour associated with brain disease in a randomized, crossover trial. Of 11 patients, brain disease was caused by brain injury, anoxia, or encephalitis in seven of them. A significant reduction in assaultive behaviour was demonstrated during treatment with pindolol.

Greendyke (1986) investigated the effectiveness of the beta-blocker, propranolol, for the improvement of behaviour associated with brain disease in a randomized, crossover trial. Significantly fewer assaults and attempted assaults occurred during the 11-week propranolol treatment as compared to the 11 weeks of placebo, $F(1,7) = 6.50$, $p < 0.05$. Of the nine patients, five showed marked improvement, two demonstrated moderate improvement, and two showed little or no improvement of assaultive behaviour.

Following the acute stage of recovery, 21 closed-head-injured (CHI) patients were treated with a maximum dose of 420 mg/day of propranolol (Brooke et al., 1992). The

intensity of agitated symptoms decreased but not the frequency, suggesting that the drug helps to reduce the emotional intensity of agitated responses.

3.3.3.5 Methylphenidate

Q21. What is the evidence supporting the efficacy of methylphenidate for aggressive behavior post ABI?

Answers
1. There is Level 2 evidence to suggest that treatment with methylphenidate following brain injury can significantly reduce anger as measured using several anger outcome measures.
2. Overall, it has been shown that anger may be reduced following brain injury with methylphenidate treatment.

Discussion
One randomized controlled trial examined the effect of methylphenidate on the control of anger following a brain injury (Mooney & Haas, 1993). They demonstrated that methylphenidate helped *to* significantly reduce anger following brain injury as demonstrated using several anger outcome measures. Despite the differences between the groups on one anger measure, a significant group main effect for the drug treatment was demonstrated.

3.3.3.6 Selective Serotonin Reuptake Inhibitor

Q22. What type of medication is sertraline and how does it work to control aggression post ABI

Answer
1. Sertraline (Zoloft) is a selective serotonin reuptake inhibitor (SSRI).
2. Since decreased serotonin is associated with both depression and aggression after brain injury, sertraline has been proposed as an effective treatment for alleviating these problems (Kant et al., 1998; Fann et al., 2000)

Q23. What is the evidence for Sertraline in the management of aggression post ABI?

Answer
1. There is Level 2 evidence that sertraline does not affect arousal and alertness.
2. There is Level 2 evidence that the use of sertraline for depression also improves cognitive performance.
3. Based on 2 non-RCT studies, there is Level 2 evidence that sertraline significantly improves depression, irritability, aggression, psychological distress, anger, functioning, and postconcussive symptoms.

4. There is Level 2 evidence based on one non-RCT that sertraline HCL decreases the incidence of aggressive behaviours.
5. Overall, Sertraline may improve depressive symptoms, psychological distress, and aggression, but it does not improve arousal.

Discussion

Kant et al. (1998) found sertraline, a serotonin specific reuptake inhibitor, was effective in reducing aggression and irritability in brain injured patients.

Meythaler et al (2001) carried out a controlled trial on 11 patients with severe TBI from motor vehicle crashes randomized to receive either sertraline or placebo. The Orientation Log, Agitated Behaviour Scale, and Galveston Orientation and Amnesia Test were used to assess their arousal and alertness. Both groups experienced similar rates of improvement on all three scales.

An 8-week nonrandomized, single-blind, placebo run-in trial by Fann et al.(2001) assessed the effects of the antidepressant sertraline on the cognitive performance of fifteen patients diagnosed with TBI and depression. Improvements in psychomotor speed, recent verbal memory, recent visual memory, general cognitive efficiency, and self-perception of cognitive symptomatology were found.

In another nonrandomized, single-blind, placebo trial, Fann et al. (2000) assessed the effects of sertraline on 15 patients diagnosed with major depression after TBI. Statistically significant improvements were found for depression, psychological distress, anger, functioning, postconcussive symptoms, and aggression. Similar results for aggression were also discovered in a multiple baseline design by Kant et al. (1998), in which positive improvements regarding irritability were found as well.

Following a multiple baseline procedure, Kant et al (1998) examined the effect of sertraline HCL (zoloft) on reducing aggression and irritability in 13 brain injured patients (5 mild, 6 moderate and 2 moderate-severe) two years post-injury. Patients were started on “50 mg/day dose that was adjusted during follow-up visits to a maximum tolerable dose or up to 200 mg per day” (results were reported for baseline, 4 and 8-week follow-up). Three patients dropped out of the study (reasons and subject characteristics were not reported). Positive effects were reported to occur (i.e., decrease in reported aggression and irritability) at each follow-up visit compared to baseline. Rater was not blinded.

3.3.3.7 Tricyclic Antidepressants

Q24. What is the evidence for the use of Amitriptyline in the management of agitation and aggressive behavior?

Answers

1. There is Level 2 evidence based on one non-RCT that amitriptyline decreases the incidence of aggressive behaviours.
2. Overall, amitriptyline may be used to decrease aggressive behaviour.

Discussion
Mysiw et al. (1988) examined the effect of amitriptyline (a tricyclic antidepressant with both serotonergic and noradrenergic reuptake inhibition) on decreasing agitation while the individual was still experiencing post-traumatic amnesia. Mysiw et al. (1988) administered amitriptyline to 20 brain injured patients, if after one week they had not responded favourably to standard behavioural intervention (i.e. where agitation persisted to the point of interfering with rehabilitation). Results indicated that within 7 days of amitriptyline therapy (mean dosage was 75 mg), 90% of the patients had a dramatic decrease in agitation with no concomitant increase in cognitive difficulties (as measured by the Orientation Group Monitoring System).

3.3.3.8 Trazodone

Q25. What is the evidence for the use of Trazodone in the management of agitation and aggressive behavior?

Answers
There is evidence that early treatment with Trazodone is a safe and effective treatment for controlling agitation post TBI.

Discussion
Trazodone is antidepressant with a sedation effect and may be useful for the treatment of insomnia after TBI (Silver & Arciniegas, 2007). According to Rosati (2002) it was evaluated in a single group intervention of 11 patients who were treated with various medications, including trazodone early for agitation post-TBI. It was found as effective administration for early treatment of post-traumatic brain injury agitation. According to the ERABI (2008), there is Level 4 evidence that early multiple neuropharmacological treatment that including trazodone may be effective for agitation after TBI.

3.3.3.9 Amantadine

Q26. What type of medication is amantadine?

Answers
1. Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and was originally used as an antiviral treatment for influenza. However, it was fortuitously noted to improve the symptoms of Parkinson's disease.
2. It is a dopaminergic medication, believed to enhance dopamine levels through both presynaptic and postsynaptic effects (Napolitano et al., 2005)
3. During the early stages of recovery from a brain injury, when intracranial pressure is increased, amantadine should be used with caution (Levy et al., 2005)

Q27. What evidence is there that amantadine is effective in treating behavioral issues post ABI?

Answer
1. The benefit of Amantadine in treating behavioural issues remains unclear.

Discussion
In a study by Green et al. (2004) in pediatric patients, despite having a significantly lower initial GCS score (amantadine group = 5.6 ± 2.5 vs. control group = 7.4 ± 3.7; p-value < 0.01) and admission Ranchos Los Amigos score, the amantadine group still experienced improvements. These included increased alertness, initiation, and verbalization and decreased agitation. Schneider et al. (1999) completed a double blinded, randomized placebo controlled trial evaluating the effects of amantadine on cognition and behavior. Twenty patients were included in the study and each took amantadine for 2 weeks. Statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behavior, and orientation did not demonstrate any significant effect for the use of amantadine.

3.3.3.10 Methotrimeprazine (Nozinan)

Q28. What type of medication is methotrimeprazine?

Answers
1. Methotrimeprazine (Nozinan) is a psychotropic medication with antipsychotic (mediated by dopamine blocking), tranquilizing, and analgesic properties. It appears to have an effect on opiate (pain) receptors as well.

Q29. What evidence is there that methotrimeprazine is effective in treating behavioral issues post ABI?

Answer
1. There is Level 4 evidence that in most cases methotrimeprazine is safe and effective for controlling agitation after ABI.

Discussion
The oral administration of methotrimeprazine (MTZ) for agitation, in doses of 2-50 mg for a maximum of 4 times per day, was evaluated in a retrospective chart review of 56 patients out of a series of 110 patients admitted for rehabilitation (Maryniak et al., 2001). This was the first report on MTZ's use in treating agitation after ABI and the authors found that in most cases MTZ was both safe and effective for controlling agitation.

3.3.3.11 Lithium Carbonate

Lithium carbonate is most commonly used for bipolar disorder. It has also been used to treat hypomania and affective instability in individuals with brain injuries, as well as aggressive behavior in non-brain-injured and mentally retarded individuals. Seizures are one of its main reported side effects (Glenn et al., 1989).

Q30. What evidence is there that lithium carbonate is effective in treating aggressive behavior?

Answer

1. It has been suggested that lithium carbonate is useful for treating evidence behavior and affective instability after ABI. However, it has the potential to cause neurotoxicity.

Discussion

10 brain-injured patients were treated for aggressive behavior, or affective instability, with lithium carbonate (Glenn et al., 1989). In this case series, 5 patients experienced a significant improvement, 1 experienced a modest improvement, 1 regressed after 7 weeks, and 3 experienced neurotoxic side effects. The authors concluded that lithium carbonate can be useful for treating aggressive behavior and affective instability after brain injury, but it can also cause neurotoxicity. Similarly, Bellus et al (1996) demonstrated effectiveness of lithium treatment for reducing aggressive and inappropriate behaviours in two, male patients.

3.3.3.12 Haloperidol

Haloperidol is a psychotropic drug found to reduce agitation. It also blocks or disrupts dopamine receptors. Thus, while it improves agitation, there is a theoretical concern it may impede recovery by reducing arousal.

Q31. What evidence is there that haloperidol is effective in treating aggressive behavior?

Answer

1. There is Level 4 evidence that haloperidol does not have a negative effect on the success of rehabilitation.

Discussion

In a retrospective chart review, agitation was managed in eleven patients with haloperidol and in fifteen patients without haloperidol (Rao et al., 1985). No differences were found between the two groups with regards to success of rehabilitation outcome.

Further Discussion: Medication Management for Behavioural Issues Post ABI:
Although several medications have been given to reduce agitation, aggression and depression following an ABI, there is little quality research done examining the effectiveness of these medications. Pharmacological management of episodic behavioural and emotional dyscontrol may include: anticonvulsants, methylphenidate, serotonin reuptake inhibitors (SSRI), beta-blockers, and tricyclic antidepressants (Bayley et al., 2007b). The following is a list of medications that have been investigated (Rees et al., 2008; van Reekum et al., 2008).

Table 3: Medication given to reduce behavioural issues post ABI

Medication given to address behavioural issues post ABI	Reason	Amount Given	Effect	Levels of Evidence
Amantadine (Schneider et al., 1999; Nickels et al., 1994)	To improve behaviour and cognitive functioning post ABI		Amantadine was not found to be effective in treating agitation post injury.	Level 2
Carbamazepine (Azouvi et al., 1999a)	To treat aggressive behaviour post ABI	A mean dose 9.47 ± 2.9 mg/kg/day of carbamazepine was given for 8 weeks	Was not shown to be effective in treating agitation following an ABI.	Level 4
Lamotrigine (Chahine & Chemali, 2006; Pachet et al., 2003)	In this case study lamotrigine was given as a mood stablizer	Medication given to each patient varied. Doses ranged from 125 mg daily to 300 mg daily. Lamotrigine was also given in combination with other medications	Lamotrigine was found to assist in reducing unwanted behaviours such as verbal aggression.	Level 5 (Limited)
Valporic Acid (Wroblewski et al., 1997)	Patients were given valporic acid post injury to reduce challenging behaviours	In the current study 5 patients were given valporic acid. 750 mg to 1500 mg was given daily along with a valporic acid serum concentrate of 35 to 110*ug*/ml to was also administered. Doses varied with each patient.	Valproci acid was found to decrease the incidence of aggressive behaviours post injury	Level 5 (Limited)
Divalproex (Chatham Showalter & Kimmel, 2000)	Divalproex was given to reduce agitated behaviour (biting, profanity, punching etc)	A mean daily dose of 1257mg of divalproex was given to patients	The incidence of aggressive behaviours was decreased	Level 4
Although there is some evidence to support using anticonvulsants to address aggressive behaviours post ABI, more research needs to be done to understand their effectiveness.				
Medication given to address behavioural issues post ABI	**Reason**	**Amount Given**	**Effect**	**Levels of Evidence**
Sertraline (Kant et al., 1998; Mysiw et al., 1988)	To reduce aggression and irritation post injury.	Sertraline HCL was given to patients- up to 200 mg daily up to 8 weeks. Amitriptyline was given for 8 weeks.	A decrease in aggressive behaviour was found following the administration of the medication.	Level 4
Pindolol (Greendyke & Kanter, 1986)	To improve behaviours following an ABI.	Subjects received 60 mg daily of pindolol daily for 10 days then the medication was increased to 100 mg in	Pindolol was found to decrease aggressive behaviour following post injury.	Level 1

		an attempt to see which dose would be more effective.		
Propranolol (Greendyke et al., 1986)	To reduce agitation.	Medication began at 60 mg daily and was increased by 60 mg per every 3 days to 420 mg	Propranolol was found to reduce agitated symptoms post injury.	Level 1
Buspirone (Levine, 1988)	To reduce agitation and anxiety.	Patient began taking 5mg 3x/day of buspirone but after 2 days this was increased to 10mg 3x/day.	Buspirone may be effective in reducing symptoms of agitation post ABI	Level 5 (Limited)
Quetiapine (Kim & Bijlani, 2006)	To treat aggressive behaviours post ABI	The amount of medication given ranged from 25 to 300 mg daily	Quetiapine was found to reduce aggressive behaviours but due to the small sample size (n=7) more research is needed.	Level 4
Ziprasidone (Noe et al., 2007)	To decrease agitation.	Medication ranged from 20mg/day to 80mg/day. Patients were on medication for a period of 35 to 68 days.	Aggression and disinhibition scores on the Agitated Behavior Scale decreased within the first 14 days of patients being put on the medication	Level 4
Lithium Carbonate (Bellus et al., 1996; Wroblewski et al., 1989)	To stabilize mood as it is believed that mood disorders may lead to aggressive behaviors	Dose varied depending on the patient.	Aggressive behaviors decreased without any evidence of a decrease in cognitive or motor behavior	Level 5 (Limited)
Medication given to address behavioural issues post ABI	**Reason**	**Amount Given**	**Effect**	**Levels of Evidence**
Medroxyprogesterone (Emory et al., 1995)	Sexually disinhibited behaviour	400 mg given 1 x per week, along with monthly psychoeducational counseling	Given intramuscularly was found to reduce sexual aggression	Level 4
Methotrimeprazine (Maryniak et al., 2001)	To reduce agitation	2-50 mg was administered up to 4 x daily	Was felt to be safe and effective in controlling agitated behaviour.	Level 4
Methylphenidate (Whyte et al., 2004; Mooney & Haas, 1993)	To control anger post injury	2 studies were conducted. In these studies methylphenidate was	Methylphenidate may be effective in increasing speed and in reducing	Level 1 Level 2

		administered post injury: to assess its effectiveness in treating processing speed, work task attentiveness and reducing anger.	anger post injury	
Droperidol (Stanislav & Childs, 2000)	To assist in calming agitated behaviour post injury	Single dose given intramuscularly (1.25 to 10 mg) for episodes of acute agitation.	Time to achieve calming was 27 minutes following an injection of droperidol compared with haloperidol, lorazepam or diphenhydramine.	Level 4
Haloperidol (Rao et al., 1985)	To assist with the reduction of agitation	2 to 15 mg/day of haloperidol was given for 14 to 62 days.	Haloperidol was not found to have a negative effect on the success of rehabilitation.	Level 4

Q32. What medications would be recommended to help him sleep?

Although many medications may be given, there is very little in the literature discussing their effectiveness with the ABI population. Concerns arise with using lorazepam and zopiclone long term, such as dependency or abuse of the medications. Caution is recommended with prescribing any of these medications.

Table 4: Pharamacological treatments to assist with sleep post ABI

Medication	Reason	Amount Given	Effect	Level of Evidence
Methylphenidate (Al-Adawi et al., 2006)	To assist those with an ABI in improving their sleep/wake cycles.	5 to 10 mg was given at 8 am and 2 pm.	Methylphenidate was not found to be effective in improving the sleep-wake cycle of those who have sustained a TBI.	Level 2
Lorazepam and Zopiclone (Li Pi Shan & Ashworth, 2004)	Medications were given to assist with sleep disorders resulting from the ABI.	0 to 1 mg/day PRN of lorazepam was given. 3.75 to 7.5 mg PRN of zipiclone was given.	Both lorazepam and zopiclone are effective in assisting with insomnia symptoms post ABI.	Level 1

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