

**Interventions for alcohol-related brain damage (ARBD): Do specific approaches
restrict the evolution of comprehensive patient care?**

Running head: Interventions for alcohol-related brain damage (ARBD)

Lindsay Horton^{1,2}

Tim Duffy¹

and

Colin R. Martin^{1,3,4}

¹School of Health, Nursing and Midwifery, University of the West of Scotland, Ayr UK,

²Loretto Care, Glasgow, Scotland, ³Faculty of Society and Health, Buckinghamshire New

University, Uxbridge, Middlesex, UK, and ⁴West London Mental Health NHS Trust, London,

UK.

Address for correspondence:

Professor Colin R Martin

Room 2.11

Faculty of Society and Health

Buckinghamshire New University

Uxbridge Campus

106 Oxford Road, Uxbridge, Middlesex, UB8 1NA, UK.

Tel: 01494 522141 Extension 2349

Fax: 01494 603179

Email: colin.martin@bucks.ac.uk

Abstract

Aims: The prevalence of alcohol-related brain damage (ARBD) is recognised to be increasing in the Western world. The aim of this paper is to review the evidence concerning interventions in ARBD.

Design and Methods: Systematic review.

Findings: 469 papers were identified of which 49 of which were suitable for inclusion. 20 concerned neuropsychological interventions; 5 detailed psychosocial interventions; and 24 focussed on pharmacological interventions. The findings suggest that a range of cognitive rehabilitation strategies can facilitate new learning and improve memory functioning, whilst psychosocial interventions and supported accommodation can improve mental and physical health

Conclusions: This review demonstrates the need for a comprehensive approach to ARBD rehabilitation and indicates that the management of this condition has not been investigated in a holistic manner.

Keywords: Alcohol-related brain damage; neuropsychology; pharmacotherapy; psychosocial interventions;

Introduction

In the last few decades, the prevalence of ARBD has been recognised to be increasing in the UK (MacRae & Cox, 2003), and it has been postulated that higher levels of alcohol consumption in recent years may lead to significant increases in the incidence of alcohol-related dementia in future generations (Gutpa & Warner, 2008). However as ARBD is currently under-diagnosed, estimates for the prevalence of the condition are thought to be imprecise (Wilson, 2013). Coupled with a lack of existing epidemiological data, specialist ARBD services are scarce (Thomson et al, 2012a; Thomson et al, 2012b; Thomson et al, 2013) and there is currently a lack of clinical guidance for the management of individuals with ARBD (Scottish Intercollegiate Guidance Network [SIGN], 2003; National Institute for Clinical Excellence [NICE], 2011). It has been estimated that approximately 25% of individuals with ARBD will make a complete recovery, whilst a further 50% will recover to some degree (Smith & Hillman, 1999). Thus, the majority of individuals with ARBD have the potential for rehabilitation, providing they maintain abstinence from alcohol (Wilson, 2011). Despite this, the fragmented nature of services, together with the lack of clear pathways of care, have been recognised as major barriers to the provision of suitable interventions for people with ARBD (Wilson, 2011; Thomson et al, 2012b). It is therefore apparent that health and social care services must be improved to ensure that coordinated ARBD care that facilitates recovery and promotes independence is available to this client group (Thomson et al, 2013).

ARBD is a heterogeneous condition, which affects memory and executive functioning and is associated with a number of comorbid health problems such as alcoholic liver disease, gastrointestinal problems, nutritional deficiencies, anxiety and depression (Cox et al, 2004; Zahr et al, 2011; Thomson et al, 2012b). The impact of ARBD is multifaceted and includes impairments in a number of domains, including cognitive, psychosocial and behavioural functioning (Kopelman et al, 2009). Despite this, the lack of integration between within health and social care services can result in people with ARBD becoming 'stuck' within a particular type of service that does not comprehensively address all of their needs (Cox et al, 2004). A multidisciplinary approach is therefore required to ensure that services offer client-centred

interventions that are tailored to meet the varying needs of individuals with ARBD in a holistic way (Kopelman et al, 2009).

The highest prevalence of ARBD is found in people between the ages of 50 and 60 years old (MacRae & Cox, 2003). Moreover, anecdotal evidence from practitioners in the field suggests that the age of onset for ARBD may be reducing. Whilst the majority of individuals diagnosed with ARBD can be expected to improve to some degree, it is estimated that around 25% will require on-going residential care or access to supported accommodation services (Smith & Hillman, 1999; Cox et al, 2004). However, a report by the Mental Welfare Commission for Scotland (2010) demonstrated that mainstream care homes for older people do not adequately meet the needs of people with ARBD. In particular, traditional care homes for older people may offer little opportunity for rehabilitation, which can lead to further functional losses and exacerbate co-morbid mental and physical health problems in people with ARBD (Wilson et al, 2012). Moreover, Kopelman et al (2009) argued that dementia services are not equipped to meet the needs of younger adults with ARBD. It can therefore be argued that the provision of age-appropriate ARBD specific residential care should be a priority within ARBD rehabilitation services.

The Arbias (2011) 'Looking Forward' handbook recommends the implementation of individualised intervention strategies for people with ARBD which incorporate techniques to address memory impairment and executive dysfunction, whilst promoting healthy eating, supporting positive behaviours and facilitating independence. Consistent with these recommendations, a number of specialist ARBD services have been set up within Scotland (Thomson et al, 2012b). The aim of this paper is to systematically review the evidence concerning ARBD interventions to enable us to make recommendations for best practice within ARBD rehabilitation services. This review will provide an overview of the range of interventions currently available for individuals with ARBD. Moreover, it will identify gaps in the evidence-base and highlight areas for future research. This review is underpinned by a holistic person centred philosophy of care. Thus, it will focus on identifying a comprehensive

range of interventions, which can be tailored to meet the needs of individual service users.

Method

An online database search was conducted on July 18 2013. The following online databases were searched to identify English language journal articles focussing on interventions for ARBD: CINAHL Plus with Full Text; Health Source: Nursing/Academic Edition; MEDLINE; Psychology and Behavioral Sciences Collection; PsycINFO. Please see Figure 1 for a PRISMA Flow Diagram depicting the literature search strategy (Moher et al, 2010). No date limitations were set in order to identify all relevant online publications and search terms included: alcohol-related brain damage/Korsakoff*/ Korsakoff's syndrome/Wernicke-Korsakoff" AND intervention*/treatment/rehabilitation.

FIGURE 1. ABOUT HERE

The database search revealed a total of 469 references. Once duplicates had been removed, 366 references remained. Two-hundred and sixty-five of these references were excluded, leaving a total of 101 abstracts to be screened for inclusion in the review. The identified papers were screened according to the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Primary research study, literature review
2. Human participants study
3. English Language paper
4. Participants have Korsakoff's syndrome
5. Papers focus on interventions rather than diagnosis or assessment of ARBD

Exclusion Criteria:

1. Animal studies
2. Acute treatment for Wernicke's encephalopathy
3. Letter, descriptive paper
4. Book reviews
5. Article focusses on the prevention of Wernicke-Korsakoff's syndrome
6. Article focusses on participants in the acute Wernicke's encephalopathy stage

Of the 101 abstracts screened, 28 were excluded as they were not relevant to this review. Seventy-three articles remained. As 1 of these papers was unobtainable, 72 were screened for eligibility. Thirty-two of these papers did not meet the inclusion criteria, leaving a total of 40 articles to be included in the review. A further online search conducted on August 28 2013 identified one additional paper for inclusion in the current review (Svanberg & Evans, 2013). An additional 8 relevant papers were identified within Svanberg and Evans' paper, and these papers have been incorporated into the current review. This left a total of 49 articles to be included in the current review: Twenty of the papers concerned neuropsychological interventions, whilst 5 focussed on psychosocial interventions and 24 detailed pharmacological treatments for ARBD. **The third author corroborated the findings of the search conducted by the first author through replication of the search strategy, detailed review of abstracts screened, and review and discussion of included papers against search criteria.**

Results

Neuropsychological Interventions

Table 1. presents details of the neuropsychological and psychosocial interventions identified within this review. The majority of the neuropsychological intervention strategies focussed on the use of cognitive rehabilitation techniques to improve cognitive functions such as memory and executive functioning. A range of memory rehabilitation techniques were identified including rote learning; visual imagery; cued

learning; verbal mediation; semantic and elaborative processing; 'imprinting' using paired associates learning; differential outcomes training; errorless learning; effortful learning; self-performed tasks and reality orientation. Compensatory strategies were also identified as a means of supporting residual memory function and compensating for cognitive impairments. Furthermore, executive functioning was targeted using strategies such as rule provision; decision-making and initiative training; and mental flexibility training. As Svanberg and Evans (2013) recently reviewed the evidence for neuropsychological ARBD interventions, the papers included in their review have been marked with an asterisk in Table 1.

TABLE 1. ABOUT HERE

Memory Rehabilitation Techniques

Cermak (1975), Goldstein and Malec (1989) and Kashima et al (1998) focused on the use of rote learning as a means of facilitating the learning and retrieval of specific information in patients with Korsakoff's Syndrome (KS). The findings from these 3 studies were variable, with Kashima et al (1998) and Goldstein and Malec's (1998) findings suggesting that the use of simple repetition is effective in training KS patients to remember specific information, whilst Cermak's (1975) findings indicated that rote learning was less effective than visual imagery and cued learning in facilitating KS patients' retrieval of verbal information. As there was no control group or comparison intervention in Kashima et al's (1998) study, their findings provide no evidence to indicate how effective simple repetition is in comparison to other strategies. Thus, Cermak's (1975) finding that rote learning was less effective than visual imagery and cued learning appears to be of greater value.

Cermak (1975; 1980) investigated the effectiveness of visual imagery and cued learning as memory improvement strategies for 6 KS patients. Cermak's findings indicated that the use of mental visualisation was more effective than either cued learning or rote learning in facilitating memory for verbal information. However,

Cermak stated that these strategies were unlikely to result in the long-term retention of information. Moreover, the generalizability and clinical applicability of Cermak's findings can be questioned, due to the small sample size and experimental nature of the studies. In a more applied study, Heinrichs et al (1992) used letter-fragment cueing to enable a hospitalised KS patient to learn and remember their activity schedule within the ward. Cueing was found to be an effective learning strategy, as it enabled the patient to respond spontaneously to unanticipated changes in the ward schedule and also showed potential as a transferable strategy, which could be used in other learning tasks. However, Heinrichs et al's findings may also be of limited generalizability as they are based on a single participant.

Cermak (1980) also investigated the use of verbal mediation and the semantic analysis of words as memory improvement strategies for 6 KS patients. The use of verbal labels in this study was found to improve the retention of random shapes, whilst analysing the meaning of words was found to facilitate their retrieval. Consistent with this, Van Damme and d'Ydewalle (2008) provided further evidence for the effectiveness of semantic processing, as elaborative processing of semantic information was found to improve 8 KS patients' memory to the level of healthy controls. Svanberg and Evans (2013) noted that Van Damme and d'Ydewalle's study provided the highest level of evidence and recommended that individuals with ARBD should be given support to make explicit associations during learning tasks, as well as being provided with rule explanations, and extra processing and retrieval time.

Hochhalter et al (2000) and Hochhalter and Joseph's (2001) studies demonstrated that differential outcomes training improved face recognition in 4 KS patients. During the differential outcomes procedure, participants learned to associate specific reinforcers with particular faces, as they were given a coin each time they correctly identified one face, whereas they were given a point for correctly identifying another face. The findings from these studies suggest that the principles of operant conditioning can be used to promote memory improvements in ARBD. Moreover, Hochhalter and Joseph (2001) stated that differential outcomes training may have real-world applications. Nonetheless, there is currently a lack of evidence to indicate

how the differential outcomes procedure can be implemented effectively within clinical settings.

Another memory improvement strategy which may have therapeutic potential within an ARBD rehabilitation context is the use of self-performed tasks (SPTs; Mimura et al, 1998; Mimura et al, 2005). Mimura et al (1998) compared the effect of STPs and verbal tasks (VTs) on memory performance and demonstrated that a sample of 8 KS patients remembered action phrases, such as 'bounce the ball,' significantly better when they enacted them during encoding. A more recent study by Mimura et al (2005) investigated the impact of self-generated SPTs, which involved 8 KS patients verbally generating their own action phrases and then performing them. The findings from Mimura et al's (2005) study also indicated that the physical enactment of verbal instructions resulted in better recall and recognition than when participants simply listened to the action phrases. Moreover, as self-generated SPTs also facilitated the recall of information, Mimura et al's (2005) findings have implications for real-life situations where the actions to be performed are chosen by the individual themselves, rather than being predetermined by another person. Consistent with this, Svanberg and Evans (2013) noted that self-generation and enactment may facilitate personal goal setting during client centred interventions.

Wilson et al (1994), Komatsu et al (2000) and Kessels et al (2007) compared the impact of errorless learning and trial-and-error learning on electronic aid programming, face-name association and route learning. Wilson et al (1994) found that errorless learning improved 5 KS patients' ability to programme the electronic device, whilst Komatsu et al (2000) demonstrated better name-face recall when errorless learning was used with 8 KS patients. In contrast, Kessels et al (2007) found no advantage of errorless learning over trial and error learning during a route learning task, which involved training 10 KS patients to remember pre-determined routes within the grounds of a hospital. The findings from these 3 errorless learning studies were inconsistent and suggest that errorless learning may facilitate the effective use of assistive technology, as well as enhancing the ability to remember names and faces, whilst it may be of limited therapeutic value during spatial

procedural learning tasks. Accordingly, Svanberg and Evans (2013) concluded that errorless learning techniques may be more beneficial during verbal rather than spatial tasks.

Woods (1983) described a Reality Orientation (RO) approach, which was used to reduce levels of confusion and reorient one 68-year old female with KS to personal and non-personal information. Twice daily individual training sessions within a hospital context resulted in improved scores on a personalised memory and information test, demonstrating that the patient was able to learn specific information that was taught within the RO sessions. Nevertheless, the participant's learning had limited generalizability beyond the information that was taught. Moreover, the extent to which the observed improvements could be attributed to rote learning, clues or memory prompts was recognised to be unclear, indicating that the mechanisms by which the RO sessions were effective were ambiguous.

Interventions for Executive Dysfunction

Three papers focussed on strategies to improve executive functioning in ARBD. Bardenhagen et al, (2007) investigated the impact of four different types of rule provision on the performance of 10 males with KS during a rule induction task. The rule induction task involved using a modified Wisconsin General Testing Apparatus (WGTA), which is a wooden stimulus board with an opaque screen. Success was achieved when participants learned the implicit rule which enabled them to correctly determine the location of rewards on the stimulus board. The findings from this study indicated that performance was best when participants were provided with both alternation rules and correction rules. These findings suggest that rule knowledge is essential to reducing errors on delayed alternation and object alternation tasks. Moreover, Bardenhagen et al proposed that poor performance during rule induction tasks is due to impaired problem solving ability, rather than simply reflecting an inability to inhibit preservative errors. Svanberg and Evans (2013) asserted that the clinical applicability of Bardenhagen et al's findings are ambiguous. However, they suggested that the provision of clear rules to individuals with ARBD during

rehabilitation may reduce the incidence of preservative errors and help to structure tasks during everyday problem solving activities.

Monteiro et al (2011) incorporated decision-making and initiative training within a neuropsychological intervention programme for a single ARBD patient. A graded approach was adopted using increasingly complex real-life scenarios, such as choosing clothes, establishing daily routines, grocery shopping, and bill payment. Decision-making and initiative training was reported to increase the patient's level of daily autonomy and independence. Nevertheless, the strategies used to achieve these improvements are unclear. In the third study addressing executive functioning, Diamant and Huijsman, (1982) used mental flexibility training to reduce behavioural rigidity in a single KS patient. Diamant and Huijsman also trained psychomotor speed and memory, using tapping and peg board tests and paired associates learning. However, as the patient withdrew from this study prematurely, the duration of the reported improvements is unknown. As both of these papers were single case studies, the strength of their findings is limited.

Compensatory Strategies

External memory aids were used to compensate for impairments in cognition and memory in the papers by Davies and Binks (1983), Lenanne (1986), Morgan et al (1990) and Montiero et al (2011). In Montiero et al's study, the use of personal journals facilitated access to newly acquired personally meaningful information and also improved temporal orientation. Moreover, Davies and Binks (1983) reported that the use of prompt cards and notebooks reduced one patient's levels of anxiety and social embarrassment. The benefits associated with using memory aids were not specifically addressed by Lenanne (1986). Nevertheless, participants used a memory-aid book, which they carried in a bag to record information they had difficulty remembering. Morgan et al (1990) found that a programmable electronic diary had no added value in improving one patient's attendance at inpatient occupational therapy groups. As the electronic diary was introduced following the successful use of verbal staff prompts and other compensatory strategies, no

evidence was obtained for the potential impact of assistive technological devices when used in the absence of alternative compensatory strategies.

Psychosocial Interventions

Limited evidence was found for the use of psychosocial ARBD interventions, as only five papers focussed on improving this aspect of functioning (Table 1). A recent descriptive study by Wilson et al (2012) presented information about a phased psychosocial rehabilitation programme for individuals with ARBD living in the community, which aimed to enhance self-efficacy, independence and the development of life-skills. Particular intervention strategies included psychological therapies, social support and the implementation of structured activity schedules to establish daily routines. This programme was reported to be effective in promoting positive clinical outcomes, such as reducing acute hospital admissions and relapse rates, whilst it also improved cognitive functioning and the living environments of service users. Lenanne (1986) and Monteiro et al (2011) demonstrated that the implementation of fixed daily routines, along with participation in alcohol-free recreational activities can increase levels of independence and spontaneity in individuals with ARBD. Moreover, Blansjaar et al (1992) and Irvine and Mawhinney (2008) provided evidence to suggest that specialist supported accommodation is beneficial in ARBD rehabilitation, as it facilitated independence as was associated with improvements in social, physical and behavioural functioning. A case study by Morrison and Pestell (2010) provided further evidence for the importance of psychosocial ARBD interventions, as an adapted cognitive-behavioural approach enabled the patient to challenge their unhelpful thoughts and assumptions and modify their behaviour, and resulted in improved mood. However, no firm conclusions can be drawn from these studies, due to methodological limitations such as small sample sizes and the descriptive nature of the psychosocial papers.

Pharmacological Treatments

A total of 12 different types of pharmacological treatment were identified within the 24 pharmacological papers (See Table 2.).

TABLE 2. ABOUT HERE

B-Complex Vitamins

Ten papers focussed on the role of B-complex vitamins in the treatment of ARBD and thiamine was the most commonly occurring pharmacological treatment to be identified. The identified papers reported a range of doses and durations of B-complex vitamin treatment, with a recent systematic review presenting evidence to suggest that 200mg of thiamine administered daily for two days was effective in improving learning and memory in WKS patients (Day et al, 2013), whilst two reviews by Cook and Thomson (1997) and Cook (2000) indicated that high-potency parenteral B-complex vitamins should be administered for 3-5 days in the prevention of WKS, and for 1 week in the treatment of WKS. A case study by Carota & Schneider (2005) indicated that 600mg of thiamine administered daily 4 months after the initial diagnosis of WKS facilitated 'dramatic' neurological and cognitive recovery. However, Leigh et al's (1981) study demonstrated that the administration of thiamine and/or the thiamine derivative thiamine tetrahydrofurfuryldisulphide (TTFD) to 24 WKS patients over varying time periods of six weeks to two years had no beneficial effects on cognitive functioning.

The oral absorption of thiamine can be considerably impaired in WKS patients. Thus, the papers included in this review indicate that B-complex vitamins should be administered parenterally rather than orally (Cook & Thomson, 1997; Cook, 2000; Thomson et al, 2013). Consistent with this, current NICE guidelines recommend that high doses (500mg) of intravenous B-complex vitamins in the form of Pabrinex should be administered 3 times daily for 2-3 days in the treatment of acute Wernicke's Encephalopathy, followed by 100mg of oral thiamine three times daily during post-acute hospitalisation and outpatient treatment (Thomson et al, 2012b). One possible contraindication of the use of B vitamins in the treatment of Wernicke-Korsakoff's syndrome is the risk of anaphylaxis following parenteral administration of thiamine (Cook, 2000; Day et al, 2013). Nevertheless, the risk of anaphylactic shock

is reported to be extremely low and the benefits of administering parenteral B-complex vitamins are recognised to outweigh the potential risks (Cook and Thomson, 1997; McIntosh et al, 2005). It is also recommended that parenteral B-complex vitamins, infused in 50-100ml of saline, should be administered slowly over a 15-30 minute time period, to reduce the risk of allergic reaction (Cook, 2000; Thomson et al, 2012b).

Acetylcholinesterase Inhibitors

Three of the pharmacological papers investigated the role of acetylcholinesterase inhibitors in the treatment of WKS (Iga et al, 2001; Cochrane et al, 2005; Luykx et al, 2008). Acetylcholinesterase inhibitors such as donepezil and rivastigmine are used in the treatment of Alzheimer's disease and act to increase the availability of the neurotransmitter acetylcholine, which plays an important role in the cortical-hippocampal system, the neural substrate of memory (Luykx et al, 2008). Both Iga et al (2001) and Cochrane et al (2005) presented evidence to indicate that donepezil is effective in the treatment of ARBD. The case report by Iga et al (2001) demonstrated that the administration of donepezil following unsuccessful thiamine and fluvoxamine treatment was effective in reducing amnesia in a 46 year old female patient with Korsakoff's syndrome. Furthermore, daily doses of 3mg Donepezil for 1 week, followed by 15mg of donepezil thereafter, resulted in improvements in cognitive functioning and quality of life (Iga et al, 2001). Consistent with these findings, Cochrane et al (2005) reported improvements in cognitive functioning in three WKS patients as a result of 6 to 8 months of donepezil treatment. Improvements in patients' subjective wellbeing and the ability to think clearly were also reported. In contrast, Luykx et al (2008) found that rivastigmine administered to five WKS patients over 6 months had no significant impact on cognitive functioning. Although slight memory improvements were found following rivastigmine treatment, the effects were not found to be significant.

Fluvoxamine

Two papers examined the effectiveness of the selective serotonin reuptake inhibitor fluvoxamine in the treatment of WKS (Martin et al, 1989; O'Carroll et al, 1994). Martin et al (1989) compared fluvoxamine administered in doses ranging from 100mg to 200mg per day to a placebo in a 4-week double-blind cross-over trial. This study included a sample of 6 KS patients, 3 patients with dementia associated with alcoholism and 1 patient with alcoholic liver disease. Fluvoxamine treatment was found to improve episodic memory in KS patients only, a finding which Martin et al (1989) suggested may be indicative of an underlying deficit in serotonergic activity in patients with KS. Nevertheless, the findings from O'Carroll et al's (1994) subsequent double-blind cross-over trial were inconsistent with Martin et al's (1989) results, as 200mg of fluvoxamine per day was found to have no advantage over placebo in terms of improving cognitive functioning in a sample of 8 KS patients. O'Carroll et al's findings were also incompatible with the serotonergic dysfunction hypothesis highlighted by Martin et al (1989), as two of the participants in O'Carroll et al's study were reported to develop symptoms of clinical depression whilst taking fluvoxamine. The discrepant nature of these findings suggests that fluvoxamine may be of little therapeutic value in improving cognitive function in patients with ARBD. However, further research is warranted to investigate the role of selective serotonin reuptake inhibitors in the treatment of this condition.

Other drug treatments

There was limited evidence to suggest that methylphenidate (O'Donnell et al, 1986); memantine (Rustembegovic et al, 2003); DL-threo-3,4-dihydroxyphenylserine (DOPS; Langlais et al, 1988); propranolol (Yudofsky et al, 1982) and clonidine (Ferrin, 1993; O'Carroll et al, 1993) have a role in the pharmacological treatment of ARBD. O'Donnell et al (1986) found improvements in long-term memory following the administration of the norepinephrine-dopamine reuptake inhibitor, methylphenidate to 6 KS patients. However, the impact of the drug was not immediate and no short-term memory improvements were found. Moreover, although O'Carroll et al (1993) found no advantageous effect of clonidine on cognitive functioning, Ferrin (1993) reported evidence to suggest that it is beneficial

in reducing anterograde amnesia. Rustembegovic et al (2003) found that administration of the N-methyl-D-aspartate (NMDA) antagonist, memantine resulted in improved cognitive functioning in 16 KS patients. However, Rustembegovic et al screened cognitive functioning using the Mini Mental State Examination (MMSE) rather than a comprehensive neuropsychological test battery, and no other papers investigated the role of NMDA, indicating that the strength of these findings was weak.

Langlais et al (1988) found limited evidence for the effectiveness of DOPS, which acts on the neurotransmitters noradrenaline and adrenaline, as it improved performance on the Memory Passage subtest of the Wechsler Memory Scale (WMS) only. Moreover, Yudofsky et al (1982) found that the sympatholytic non-selective beta blocker, propranolol resulted in the reduction in rage and violent behaviour in one male KS patient. However, as this study was based on a single patient displaying frequent violent behavioural outbursts, this finding may not be generalizable to other individuals with ARBD. There was no evidence within this review to suggest that Desglycinamide Arginine Vasopressin (DGAVP; Jennekins-Schinkel et al, 1985); Physostigmin (O'Donnell et al, 1986); Reboxetine (Reuster et al, 2003) and Rivastigmine (Luykx et al, 2008) should be used to treat patients with ARBD.

Discussion

This review examined the evidence for ARBD interventions, with the principle aim of informing practice within ARBD rehabilitation services. The range of interventions and treatments identified within this review reflects the multifaceted nature of ARBD and highlights the need for a comprehensive approach to the management of this condition (Cox et al, 2004; Kopelman et al, 2009). Nevertheless, the disproportionate number of pharmacological and neuropsychological papers identified within the review indicates that research into psychosocial interventions for ARBD has historically been sparse, and suggests that previous research in this area has focussed mainly on treating the medical and cognitive aspects of ARBD. The lack of integration between neuropsychological, psychosocial and pharmacological research suggests that the management of individuals with ARBD has not been investigated in a holistic manner.

A range of neuropsychological interventions were identified within this review, including memory rehabilitation techniques, methods of addressing executive dysfunction and compensatory strategies. As the neuropsychological studies were mainly experimental, the findings presented within this review may have limited ecological validity, clinical applicability. Moreover, the small sample sizes limits the generalizability of these findings. Ten of the papers included in this review were single-subject case studies. This represents a significant weakness within the contemporary evidence base as it limits the extent to which the studies can be used to make evidence-based recommendations in terms of generalisability. As less than half of the neuropsychological papers were published within the last decade, it is clear that the evidence base for neuropsychological ARBD interventions needs updating. These limitations notwithstanding, the findings indicate that cognitive rehabilitative strategies can facilitate new learning and alleviate anterograde amnesia in individuals with ARBD.

The strongest evidence was found for the following cognitive rehabilitative strategies: visual imagery (Cermak, 1975; Cermak, 1980); elaborative and semantic processing

(Cermak, 1980; Van Damme & d'Ydewalle, 2008); self-performed and self-generated tasks (Mimura et al, 1998; Mimura et al, 2005); errorless learning during verbal tasks (Wilson et al, 1994; Komatsu et al, 2000); and rule provision during problem solving (Bardenhagen et al, 2007). It is therefore recommended that individuals with ARBD should be supported to make visual and semantic associations during learning. Practitioners should also provide explicit instructions and additional processing and retrieval time, as well as preventing individuals from making errors during learning. Individuals with ARBD should be encouraged to physically enact instructions and formulate their own treatment goals. Memory aids and environmental modifications should also be used in the rehabilitation of ARBD, as they can improve daily functioning and may reduce the anxiety and social embarrassment associated with memory impairment (Davies & Binks, 1983; Lenanne, 1986; Morgan et al, 1990; Monteiro et al, 2011).

Limited evidence was found for psychosocial ARBD interventions and the existing psychosocial evidence was of limited quality, due to methodological weaknesses and small sample sizes. Nonetheless, the findings from this review indicate that a variety of psychosocial interventions are beneficial in the rehabilitation of ARBD. It is therefore recommended that practitioners should deliver structured group and individual psychosocial interventions which focus on establishing regular daily routines, such as self-care habits, regular meal times and participation in timetabled activities, within an alcohol-free environment (Lenanne, 1986; Monteiro et al, 2011; Wilson et al, 2012). Many individuals with ARBD may be socially isolated (MacRae & Cox, 2003). Thus, it is also recommended that psychosocial interventions should focus on promoting family involvement, as well as encouraging the development of social support networks by facilitating engagement in meaningful social activities (Wilson et al, 2012). The reviewed evidence suggests that ARBD interventions should take place within supported accommodation facilities, as Blansjaar et al (1992) and Irvine and Mawhinney (2008) highlighted the potential value of specialist residential rehabilitation in enhancing social and behavioural functioning and improving physical and mental health. Morrison and Pestell, (2010) demonstrated the potential value of cognitive-behavioural interventions in promoting recovery from ARBD. However, these authors noted that cognitive restructuring techniques may be

problematic within ARBD rehabilitation, due to impaired memory and issues with abstract thought. It is therefore suggested that low intensity behavioural strategies, such as behavioural activation may be more beneficial in the psychosocial rehabilitation of ARBD (Williams & Martinez, 2008).

A number of pharmacological ARBD treatments were identified within this review, including thiamine and B-complex vitamins; acetylcholinesterase inhibitors; fluvoxamine and a number of other drugs for treating memory impairment. Due to small sample sizes, inconsistent results and the small number of up to date pharmacological studies, the evidence for the pharmacological management of ARBD is inconclusive. The most extensive evidence was found for thiamine treatment, with ten papers focused on the treatment of ARBD with thiamine and B-complex vitamins. Therefore, as Wernicke-Korsakoff's Syndrome (WKS) is primarily caused by thiamine deficiency (Isenberg-Grzeda et al, 2012), and as vitamin B6 and B12 deficiencies can also impair the absorption of thiamine in chronic alcoholics (Thomson et al, 2012b), the administration of B-complex vitamin supplements along with sufficient intake of dietary nutrients, is recommended in the long-term management of ARBD (Arbias, 2011). Nevertheless, there is currently no standardised protocol concerning the dosage, frequency and route of thiamine treatment for WKS and there is a recognised lack of conclusive evidence concerning the optimum duration of thiamine treatment in the long-term management of ARBD (Sum & Brody, 2012; Day et al, 2013). Moreover, as current clinical guidelines are based on the findings from basic science, case reports and methodologically weak research papers rather than robust evidence from double-blind randomised control trials (Sum & Brody, 2012; Day et al, 2013), the therapeutic value of B-complex vitamin supplements in the pharmacological management of ARBD is unclear.

This review has highlighted the need for more research into the comprehensive rehabilitation of individuals with ARBD. It can be argued that methodologically robust randomised control trials (RCTs) investigating the efficacy of specific rehabilitation strategies may be of limited clinical relevance (Mantzoukas, 2008), as the ecological validity of RCT findings may be compromised. Consistent with this, Svanberg and

Evans (2013) asserted that single case experimental studies offer a potentially fruitful means of advancing what is known about effectiveness of individual components of ARBD interventions. It is therefore recommended that applied longitudinal research employing both quantitative and qualitative research methods should be conducted, to close the gap between theory and practice and to gain a rich understanding of the therapeutic value of specific intervention strategies within a holistic model of ARBD care.

Implications for practice

Nurses, doctors and allied health professionals have a critical role in the provision of high quality care for ARBD and an understanding and appreciation of the contemporary evidence base in interventions in this area is critical to foster patient centred and high quality care. This review suggests that ARBD interventions should include a combination of cognitive rehabilitation techniques; compensatory strategies for memory impairment; psychosocial interventions and pharmacological treatments. Despite the limitations noted above, the findings from this review are consistent with the practice recommendations outlined by Arbias (2011). Due to the focussed nature of our search strategy, it is possible that this review has not captured all of the relevant evidence concerning interventions that may be of relevance to the rehabilitation of individuals with ARBD. Moreover, due to the existence of comorbid mental and physical health problems, (Cox et al, 2004; Zahr et al, 2011; Thomson et al, 2012b) it is possible that additional relevant intervention strategies may exist within the broader research literature. It is nevertheless clear that the body of research concerning comprehensive ARBD specific interventions is in its infancy. The scale of the studies reviewed within this paper is very small. The scarcity of the existing evidence is problematic as it suggests that the findings may not be generalizable and also indicates that the size of the evidence-base is currently incongruous with the increasing prevalence of ARBD. Further research is therefore warranted to ensure that ARBD rehabilitation services are evidence-based and meet service users' needs in all relevant domains.

Acknowledgements

This review was funded in part by a grant awarded by the West of Scotland Knowledge Transfer Partnership Centre, Glasgow, Scotland, UK. The authors report no conflict of interest. We are also extremely grateful to two expert reviewers for their detailed, benign and facilitative comments on an earlier version of this manuscript.

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Table 1: Neuropsychological and psychosocial interventions for ARBD

Intervention	Number of papers	Number of Case Studies	Description of intervention	Summary of findings
Rote learning	3 [3,7,12]	0	Use of repetition to facilitate learning and retrieval of information	Findings were inconsistent. Rote rehearsal improves memory for specific information only.
Visual imagery	2 [3,4]	0	Use of visualisation to create images associated with verbal information.	Visual imagery was more effective than cued and rote learning and consistently improved free recall and recognition of verbal information.
Cued learning	3 [3,8*, 21]	0	Semantic cues (Cermak, 1975) and letter-fragment cueing (Heinrichs et al, 1992) were used to aid the retrieval of information.	Cueing improved performance, but was not as effective as visual imagery in facilitating memory (Cermak, 1975). Cueing enabled KS patient to learn activity schedule, develop self-cueing skills and improve temporal orientation. Benefits were generalizable to tasks that were not specifically trained (Heinrichs et al, 1992).
Verbal mediation	1 [4]	0	Use of verbal labelling to facilitate memory for non-verbal information.	Verbal labels improved retention of non-verbal material.
Elaborative/ semantic processing	3 [4, 21, 22*]	0	Use of conceptual and contextual knowledge to aid retrieval of information.	Semantic analysis facilitated word retrieval when 12-item word lists were used (Cermak, 1980). KS patients were able to process elaborative, semantic information as well as controls if given additional time, explanation and support to do so (Van Damme & d'Ydewalle, 2008).
Differential outcomes training	3 [9*, 10*, 21]	0	Conditioning procedure using consistent and specific outcomes/reinforcers in conjunction with specific discriminative stimuli.	Accuracy for remembering faces was markedly better during differential outcomes training than during non-differential outcomes training.
Errorless learning / trial and error learning	4 [13*,14, 21, 23*]	0	Errorless learning prevents opportunities for making errors whilst learning, whilst trial and error learning provides opportunities to make errors and learn from previous mistakes whilst learning.	Findings were inconsistent. Errorless learning improved performance on a variety of tasks, including learning the names of people and objects, programming an electronic aid, remembering orientation items and acquiring new general knowledge. However, it was no more successful than trial and error learning on a spatial procedural route-learning task.
Effortful learning / effortless learning	1 [14]	0	Effortful learning involves effortful cognitive processing, whilst effortless learning does not.	Memory was enhanced during a modified version of the vanishing cues method, which was designed to reduce errors whilst still requiring effortful cognitive processing.
Self-performed tasks / verbal tasks	3 [16*, 17*,21]	0	Self-performed tasks (SPTs) involve listening to action phrases and subsequently performing the actions, whilst verbal tasks (VT) involve listening to action phrases without enacting them.	Memory for action phrases was better following SPTs than following VTs.
Self-generated SPTs/self-generated VTs	2 [17*,21]	0	Self-generated SPTs involve verbally generating an action phrase and then performing the action, whilst self-generated VTs involve verbally generating an action phrase without performing it.	Self-generation facilitated recognition whether or not the action phrase was enacted, whereas recall was enhanced only when self-generated action phrases were enacted.
Reality orientation	1 [25]	1 [25]	Presentation of information to reorient individuals to their environment and reduce levels of confusion.	Reality orientation sessions resulted in improved scores on a memory and information test.
Rule provision	2 [1*,21]	0	Alternation rules and/or correction rules were provided during delayed alternation (DA) and object alternation (OA) tasks to facilitate rule induction and response inhibition.	Rule provision improved performance in KS patients
Decision-making and initiative training	2 [18*,21]	1 [18]	Training was delivered to improve performance on increasingly difficult real-life activities, including making food choices, scheduling activities, establishing self-care habits, grocery shopping and paying bills.	Observed behavioural changes included spontaneous initiation of self-care tasks, use of memory aids, increased independence at home, and improved ability to make decisions and fulfil commitments.
Psychomotor, memory, mental flexibility training	1 [6]	1 [6]	14-week training program aiming to increase psychomotor speed (assessed using Purdue peg board and tapping test), imprinting (using paired associates learning) and mental flexibility (assessed with test of behavioural rigidity).	Improvements were found in 'most' trained functions. Imprinting/memory was the most improved function.

Compensatory strategies	5 [5,15,18*, 19* 21]	3 [5, 18, 19]	Use of notebooks, calendars, diaries, photography, lists, prompting, assistive technology and environmental modifications to compensate for cognitive and memory impairments.	Compensatory memory strategies supported residual memory, facilitated access to newly acquired autobiographical information, improved temporal orientation, enabled self-monitoring of daily activities and reduced social embarrassment and anxiety.
Supported Accommodation	3 [2*, 11, 21]	0	Nursing home, specialist supported accommodation	Findings were variable, but suggest that specialist accommodation can improve social functioning, promote family involvement, facilitate participation in meaningful activities, encourage abstinence, improve skills in activities of daily living, and improve physical and mental health.
Psychosocial rehabilitation	4 [15,18*, 21, 24*]	1 [18]	Psychosocial rehabilitation strategies included stabilisation, establishment of daily routine, skill acquisition, problem solving, nutritional maintenance, social integration and relapse prevention.	Key outcomes of psychosocial rehabilitation included reduced acute hospital admissions, abstinence from alcohol, placement in appropriate accommodation, improved cognitive and behavioural functioning, reduced social isolation, increased independence, acquisition of skills, and improved mental and physical health.

Papers: *Bardenhagen et al, 2007 [1]; *Blansjaar et al, 1992 [2]; Cermak, 1975 [3]; Cermak, 1980 [4]; Davies and Binks, 1983 [5]; Diamant and Huijsman, 1982 [6]; Goldstein and Malec, 1989 [7]; *Heinrichs et al, 1992 [8]; *Hochhalter et al, 2001 [9]; *Hochhalter and Joseph, 2001 [10]; *Irvine and Mawhinney, 2008 [11]; Kashima et al, 1998 [12]; *Kessels et al, 2007 [13]; Komatsu et al, 2000 [14]; Lennane, 1986 [15]; *Mimura et al, 1998 [16]; *Mimura et al, 2005 [17]; *Monteiro et al, 2011 [18]; *Morgan et al, 1990 [19]; *Morrison and Pestell, 2010 [20]; Svanberg and Evans, 2013 [21]; *Van Damme and d'Ydewalle, 2008 [22]; *Wilson et al, 1994 [23]; *Wilson et al, 2012 [24]; Woods, 1982 [25].

N.B. Papers marked * were also reviewed by Svanberg and Evans (2013)

Table 2: Pharmacological treatments for ARBD

Drug	No. of papers	Number of Case Studies	Description of treatment	Summary of findings
Thiamine and other B vitamins	10 [1, 3,4,5,7,12,15, 21,23,24]	2 [1,24]	B vitamins include thiamine (B1), riboflavin (B2), niacin (B3), folate (B9) and pyridoxine (B6). Dietary sources include wholemeal cereals, nuts, yeast, pulses, leafy vegetables, liver, chicken, beef, fish, pork, dairy products. B vitamins can be administered subcutaneously, intravenously, or orally.	B-complex vitamins are essential in the acute treatment of Wernicke-Korsakoff's Syndrome. However, no standardised dosage, frequency and route of thiamine treatment for WKS exists, and the optimum duration of thiamine treatment in the long-term management of ARBD is currently unknown.
Acetylcholinesterase inhibitors (AChEI) Donepezil & Rivastigmine	3 [2,8,13]	1 [8]	AChEI inhibits the neurotransmitter acetylcholine from breaking down to increase the level and duration of its action. Donepezil and Rivastigmine are used to treat Alzheimer's disease.	Donepezil was associated with improved memory, quality of life, and wellbeing, whilst Rivastigmine had no beneficial impact on cognitive functioning.
Fluvoxamine	2 [6,14,17]	0	Selective serotonin reuptake inhibitor used to treat depression.	Findings were inconsistent.
Methylphenidate	1 [18]	0	Norepinephrine-dopamine reuptake inhibitor (NDRI) known as Ritalin, which acts as a stimulant.	Methylphenidate associated with improvements in long-term memory, although the impact of the drug was not immediate. No short-term memory improvements were found.
Clonidine	1 [16]	0	α 2 Adrenergic agonist	Clonidine had no advantageous effect on neuropsychological measures in comparison to placebo.
Desglycinamide Arginine Vasopressin (DGAVP)	2 [9,10]	0	Neuropeptide which regulates the body's retention of water	No evidence to suggest that DGAVP has a beneficial effect on memory.
Physostigmine	1 [18]	0	Cholinesterase inhibitor	Administration of physostigmine alone had no beneficial effect on memory function.
DL-threo-3,4-dihydroxyphenylserine (DOPS)	1 [11]	0	Synthetic amino acid precursor which acts on neurotransmitters noradrenaline and adrenaline	DOPS improved performance on the Memory Passage subtest of the Wechsler Memory Scale (WMS) only.
Reboxetine	1 [19]	0	Selective noradrenaline reuptake inhibitor	Reboxetine had no beneficial effect on cognition.
Memantine	1 [20]	0	NMDA antagonist which blocks glutamate receptors	Memantine was associated with improved performance on the MMSE.
Propranolol	1 [25]	0	Sympatholytic non-selective beta blocker	Propranolol was associated with reduced rage and violent behaviour in male with KS.

Papers: Carota & Schneider, 2005 [1]; Cochrane et al, 2005 [2]; Cook & Thomson, 1997 [3]; Cook, 2000 [4]; Day et al, 2013 [5]; Ferrin, 1993 [6]; Hemmingsen et al, 1983 [7]; Iga et al, 2001 [8]; Jennekins-Schinkel et al, 1985 [9]; Laczi et al, 1983 [10]; Langlais et al, 1988 [11]; Leigh et al, 1981 [12]; Luykx et al, 2008 [13]; Martin et al, 1989 [14]; McIntosh et al, 2005 [15]; O'Carroll et al, 1993 [16]; O'Carroll et al, 1994 [17]; O'Donnell et al, 1986 [18]; Reuster et al, 2003 [19]; Rustembegovic et al, 2003 [20]; Sum et al, 2012 [21]; Thomson et al, 2012a [22]; Thomson et al, 2012b [23]; Yudofsky et al, 1984 [24].

Figure 1: Flow of information through systematic review

Identification

Number of references identified through database searching – 469

Number of references after duplicates removed – 366

Number of references excluded – 265

Screening

Number of abstracts screened - 101

Number of references excluded – 28

Eligibility

Number of full text articles assessed for eligibility – 73

Number of papers unobtainable - 1

Number of papers eligible - 72

Number of full text articles excluded - 32

Included

Number of papers included in review = 49

Additional papers - 9

