Psychological Medicine

cambridge.org/psm

A systematic review of treatments for alcohol-related cognitive impairment: lessons from the past and gaps for future interventions

Elsa Caballeria, Clara Oliveras, Laura Nuño, Mercedes Balcells-Oliveró, Antoni Gual and Hugo López-Pelayo

Grup Recerca Addiccions Clínic (GRAC-GRE). Department of Psychiatry, Clinical Institute of Neuroscience, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic Barcelona, RETICS (Red de Trastornos adictivos), University of Barcelona, Villarroel, 170, 08036 Barcelona, Spain

Review Article

Cite this article: Caballeria E, Oliveras C, Nuño L, Balcells-Oliveró M, Gual A, López-Pelayo H (2020). A systematic review of treatments for alcohol-related cognitive impairment: lessons from the past and gaps for future interventions. *Psychological Medicine* **50**, 2113–2127. https://doi.org/10.1017/S0033291720002925

Received: 7 October 2019
Revised: 11 May 2020
Accepted: 30 July 2020
First published online: 25 August 2020

Key words:
Alcohol brain damage; alcohol-related cognitive impairment; cognitive intervention; cognitive rehabilitation; pharmacotherapy

Author for correspondence:
Elsa Caballeria,
E-mail: caballeria@clinic.cat

Abstract

Alcohol-related cognitive impairment (ARCI) is highly prevalent among patients with alcohol dependence. Although it negatively influences treatment outcome, this condition is underdiagnosed and undertreated. The aim of this systematic review is to investigate the existing evidence regarding both cognitive and pharmacological interventions for ARCI. We systematically reviewed PubMed, Scopus and Science direct databases up to May 2019 and followed the PRISMA guidelines. The quality of the studies was assessed using the Jadad Scale. Twenty-six studies were eligible for inclusion (14 referring to neuropsychological interventions and 12 to pharmacological treatments). Among neuropsychological interventions, computerised treatments, errorless learning and component method showed positive effects on working memory, memory measures and general cognitive function. On the other hand, thiamine, memantine and methylphenidate improved working memory, long-term memory and general cognitive function. Nevertheless, these studies have several limitations, such as small sample size, lack of replication of the results or low specificity of the interventions. Therefore, no gold-standard intervention can yet be recommended for clinical practice, and further research based on promising strategies (e.g. digital interventions, thiamine) is required.

Introduction

Alcohol is considered to be a contributive factor in more than 200 health conditions (World Health Organization, 2018) and a risk factor for premature death (Rehm, Shield, Gmel, Rehm, & Frick, 2013). Much of the burden of disease is due to the persistent effects of alcohol on the central nervous system (Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016; Soler González, Balcells Oliveró, & Gual Solé, 2014). One out of 10 dementia cases is alcohol-related (Harper, 2009) with a dose–response relationship (Xu et al., 2017). Indeed, alcohol is the main modifiable risk factor for dementia (Schwarzinger et al., 2018). Alcohol-related dementia mortality is also a concern. Up to 50% of patients affected by Wernicke–Korsakoff Syndrome die due to infectious diseases and cancer in the 8 years after diagnoses (Sanvisens et al., 2017).

Alcohol can lead to structural and functional changes in the brain (Bates, Buckman, & Nguyen, 2013; Harper, 2009; Sachdeva et al., 2016). These brain abnormalities imply global atrophy (Bates et al., 2013) as well as region-specific neuronal loss in the superior frontal association cortex, hippocampus, limbic system, cerebellum, thalamus and hypothalamus and the connections between them (Harper, 2009; Oscar-Berman & Marinković, 2007; Pitel, Segobin, Ritz, Eustache, & Beaunieux, 2015; Ridley, Draper, & Withall, 2013; Sachdeva et al., 2016). White-matter loss occurs in the prefrontal cortex, corpus callosum and cerebellum (Hayes, Demirkol, Ridley, Withall, & Draper, 2016; Ridley et al., 2013). These structural changes lead to impairments in attention, memory and learning, executive functions and fluid abilities such as concept formation, visuospatial processing, abstraction or problem solving, among others (Bernardin, Maheut-Bosser, & Paille, 2014; Manning, Verdejo-Garcia, & Lubman, 2017; Moerman-van den Brink et al., 2019; Ros-Cucurull et al., 2018; Sachdeva et al., 2016; Stavro, Pelletier, & Potvin, 2013; Wanmaker et al., 2018; Woods et al., 2016).

The concept of alcohol-related brain damage becomes increasingly important. It encompasses a spectrum of disorders, including alcohol-related dementia and Wernicke–Korsakoff Syndrome (Bates, Bowden, & Barry, 2002; Hayes et al., 2016; Ros-Cucurull et al., 2018). It has been estimated that among patients with a heavy drinking pattern, dementia is present in 10–24% of the patients (Ridley et al., 2013). Despite those severe forms, mild to moderate neurocognitive deficits are prevalent among patients with alcohol use disorder, with an estimated proportion of 50–70% presenting some degree of impairment (Bates et al., 2013). Even though for most of the patients many of the neuropsychological deficits related to

CAMBRIDGE UNIVERSITY PRESS

heavy alcohol use are minimal or transient (Bates et al., 2013) and improve with sustained abstinence (Mulhauser, Weinstock, Ruppert, & Benware, 2018; Ridley et al., 2013; Ros-Cucurull et al., 2018; Stavro et al., 2013), in some cases, deficits are clinically severe and can persist (Hayes et al., 2016; Sachdeva et al., 2016). Nevertheless, the different cognitive functions do not recover homogeneously (Ioime et al., 2018; Mulhauser et al., 2018; Ros-Cucurull et al., 2018). Among other factors, the amount of recent alcohol use and duration of abstinence have an influence on the recovery of cognitive skills (Ridley et al., 2013). The accumulation of repeated episodes of binge drinking followed by periods of abstinence leads to a slower and less complete recovery (Florez, Espandian, Villa, & Saiz, 2019).

Impairments in executive functioning and memory can affect the efficacy of cognitive and behavioural treatments (Bernardin et al., 2014; Blume & Alan Marlatt, 2009; Blume, Schmaling, & Marlatt, 2005). These neurocognitive deficits may influence the patients' ability to attend and retain new information, identify goals or flexibly adapt to new environmental demands (Rupp, 2012). Moreover, cognitive deficits can be associated with increased impulsivity (Bates et al., 2002; Czapla et al., 2016; Moraleda Barreno et al., 2019) that alter decision making (Domínguez-Salas, Díaz-Batanero, Lozano-Rojas, & Verdejo-García, 2016; Moraleda Barreno et al., 2019; Stevens et al., 2015). As a consequence, patients with alcohol-related cognitive impairment (ARCI) present lower self-efficacy (Bates, Pawlak, Tonigan, & Buckman, 2006; Sachdeva et al., 2016), lower motivation and treatment compliance (Bates et al., 2013, 2006; Bernardin et al., 2014), as well as fewer days of abstinence (Florez et al., 2019; Sachdeva et al., 2016), more drinks per drinking day (US SDUs, 1SDU = 14 g) (Bates et al., 2006) and poorer quality of life (Horton, Duffy, & Martin, 2015; Rensen, Egger, Westhoff, Walvoort, & Kessels, 2017). Furthermore, the comorbidity of ARCI with other psychiatric disorders, depression for instance, can worsen the cognitive symptoms (Horton et al., 2015).

In this context, despite the potential indirect effects of cognitive impairment in treatment outcome (Bates et al., 2002, 2006; Manning et al., 2017), ARCI is still underdiagnosed (Hayes et al., 2016; Horton, Duffy, & Martin, 2014; Soler González et al., 2014), under-recognised (Sachdeva et al., 2016) and undertreated (Barrio et al., 2016; Horton et al., 2015; Manning et al., 2017).

Two previous studies systematically reviewed the available treatments for ARCI (Horton et al., 2014; Svanberg & Evans, 2013). Differently to these two previous reviews in which many of the studies were included independently of the evidence level and the vast majority were case reports or case series, the present review is aimed at the analyses of longitudinal studies that include a control group.

Hence, the aim of the present review is to examine and describe the range of neuropsychological and pharmacological interventions available for ARCI treatment.

Methods

Data for the systematic review were collected following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). This protocol provides a checklist for reporting systematic reviews (online Supplementary Table S1).

Search strategy

Electronic searches were performed by two independents reviewers (EC, HL-P) using PubMed, Scopus and Science Direct databases. A combination of the following terms was used: (alcohol-related brain damage OR alcohol-related cognitive impairment OR korsakoff OR Wernicke-Korsakoff OR Korsakoff's syndrome) AND (intervention OR rehabilitation OR remediation OR treatment). No date limitations were set, so all relevant publications could be identified. The included bibliography was reviewed in order to add studies that may be relevant but did not show up on the searches.

Selection criteria

The search resulted in 804 published articles (Fig. 1). Studies were included if (1) referred to any cognitive rehabilitation or pharmacological intervention for cognitive deficits related to alcohol; (2) were prospective interventions; (3) included a control group; (4) cognitive rehabilitation interventions among other substance users were also included as long as the alcohol users group outcomes were specified. Exclusion criteria were (1) animal studies, (2) brain structural or functional studies that do not include a cognitive outcome, (3) not available in English, Spanish, Catalan or French.

Data extraction

Data were independently extracted by four reviewers, grouped in pairs (EC and HL-P extracted data from half of the articles and LN and CO from the other half), and in case of disagreement, advice from a senior researcher was asked (MB and AG). From the selected studies, the following information was extracted: authors' names, year of publication, country where the intervention was carried, study design (randomised control trial, RCT *v.* non-RCT *v.* cohort) blinding (double blind *v.* single blind *v.* not blind), sociodemographic data of included patients (sample size, gender, age), control group (matched controls or not, and sociodemographic characteristics), main cognitive domain studied, outcome measure, main and secondary results, source of funding and limitations. Quality of the included articles was also assessed, using Jadad Scale for randomised controlled trials (Jadad et al., 1996), which assesses if randomisation has been conducted appropriately (items 1–3), the method of blinding (items 4–6) and if the fate of all the participants in the trial has been specified (item 7). The scoring anchors range from 0 to a maximum of 5.

The effect size for the findings in the included studies will be offered in the Results section. If these data are not offered in the article and enough data are available, the Cohen's *D* will be computed, using the online calculator from the University of Colorado Springs (https://lbecker.uccs.edu/). The effect sizes of the interventions presenting statistically significant results will be summarised in Table 3, together with data regarding the quality of the studies (Jadad Scale scores).

Results

From the 804 resulting articles, 26 were finally included for revision (Fig. 1). Among these, 14 were referred to neuropsychological rehabilitation interventions and 12 to psychopharmacological treatments.

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

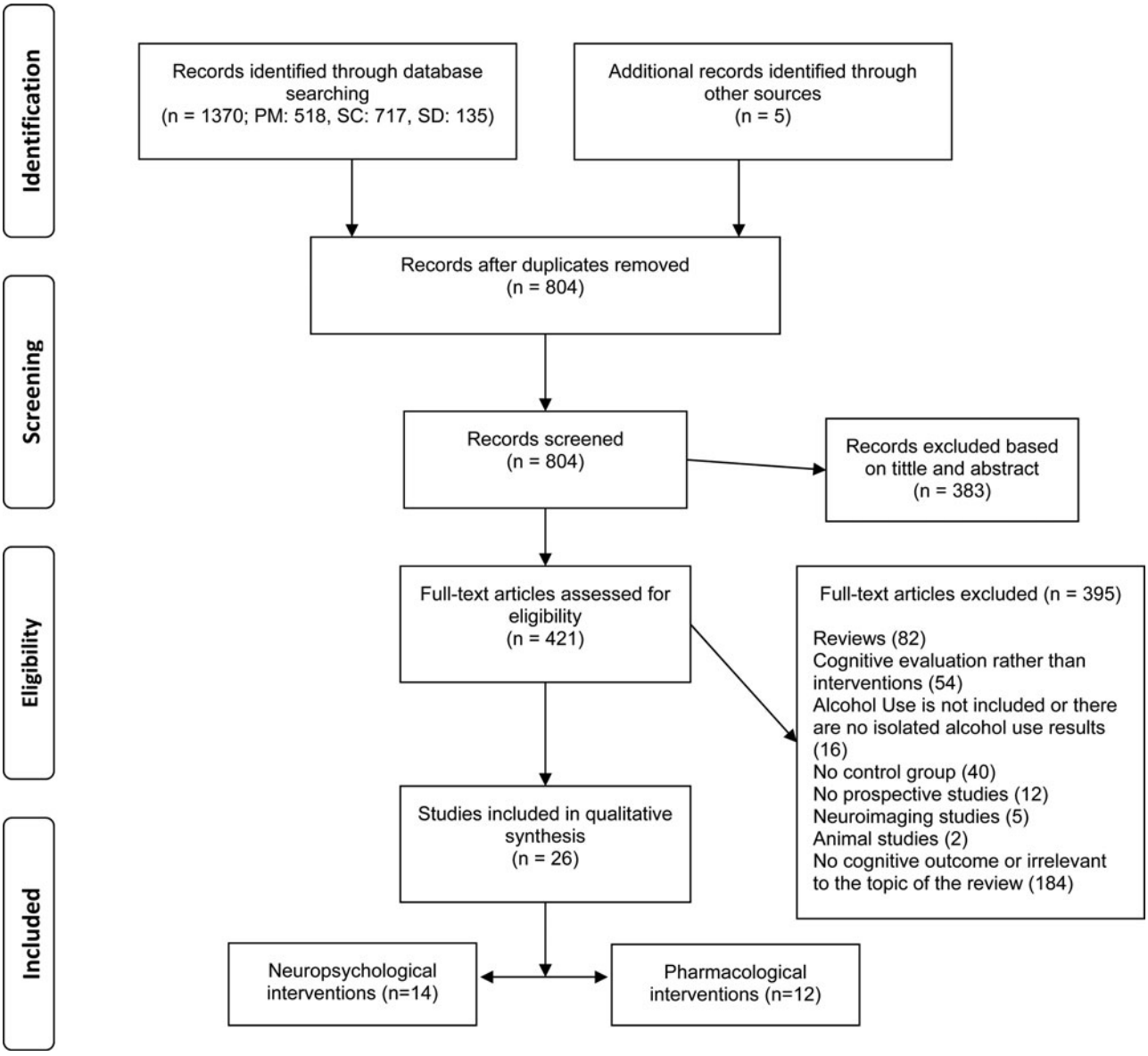

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. PM, PubMed; SC, Scopus; SD, Science Direct.

Neuropsychological interventions

Intervention will be presented according to the main strategy applied (technology-based interventions, errorless learning, component method, other interventions) (Table 1).

Technology-based interventions

Technology-oriented intervention refers to cognitive stimulation treatments that have been applied through some computer or mobile phone-based system.

Working memory/executive functions: Two studies (Khemiri, Brynte, Stunkel, Klingberg, & Jayaram-Lindström, 2019; Snider et al., 2018) were identified exploring the effect of a computer-based working memory training to strengthen working memory capacity. In these, the training was performed using the COGMED® software, which consists of 12 different verbal and visuospatial working memory exercises. The software used would adjust to the individuals' performance and progressively increase the exigency of the tasks.

COGMED® training resulted in statistically significantly greater improvement in verbal working memory but not in the spatial working memory function or in other neuropsychological tasks in 25 patients (50% male, mean age = 49.6) with the alcohol use disorder diagnoses (severity = unspecified) that were not receiving treatment (active drinking) in comparison to the matched control group (partial $\eta^2 = 0.142$) (Khemiri et al., 2019). As shown by the results, working memory training using this tool enhanced performance on a near-transfer task in 20 patients (68% male with a mean age = 42.5 years old) with alcohol dependence who reported drinking during the previous 6 months ($r^2 = 0.15$) (Snider et al., 2018).

Furthermore, cognitive training was also related to behavioural changes as a trend was found between working memory training and the reduction of drinks per drinking occasion (from 7.07 drinks to 5.58 drinks in the intervention group *v.* 5.58 drinks to

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

Table 1. Neuropsychological interventions for alcohol-related cognitive impairment (ARCI)

Ref.	Design	Double blind	EG (M/F); age mean (SD)	CG (M/F); age mean (SD)	Diagnose	Intervention	Control intervention	Follow-up	Neuropsychological instrument	Main outcome	Secondary outcome	Jadad (0–5)
Technology-based interventions												
Working memory/executive functions												
(Khemiri et al., 2019)	RCT	Yes	25 (13/12);49.6 (6.1)	25 (12/13); 49.8 (8.7)	AUD[a] (active drinking)	5 weeks. Adaptive 12 WM training tasks (COGMED®)	No data	No, post treatment	CANTAB	Digit span task improved only in the active group ($t = 6.12$, $p = 0.018$)	Active group decreased number of drinks/drinking day	4
(Snider et al., 2018)	RCT	Single	25 (17/8); 42.5 (2.0)	25 (17/8); 42.4 (2.3)	AD[a]	20 sessions. Adaptive WM tasks (COGMED)	COGMED® WM training. No more progression than level 2	No, post treatment	Near transfer task; DD task; Far transfer task (EFT)	Improved performance in a Near transfer task for the EG ($t48 = 2.65$; $p = 0.011$)	No other differences between groups	3
Verbal learning and verbal memory												
(Bell et al., 2016)	RCT	No	15 (14/1); 55.27 (5.27)	16 (16/0); 55.06 (5.23)	AUD[b] (30 first days of abstinence)	Posit Science software® 5 h/week 13 weeks. Tasks that adapted its difficulty + work therapy + group sessions	Work therapy without cognitive training	3 months, 6 months	HVLT. Verbal memory (HVLT Total *T* Score); verbal learning (HVLT trial 3 *T* score)	Improved verbal memory ($F_{(1, 28)} = 7.98$, $p < 0.01$) and verbal learning ($F_{(1, 28)} = 9.22$, $p < 0.005$) at 3 months FU	Improvement maintained in verbal memory ($F_{(1, 28)}$ D 10.73, $p < 0.005$) and verbal learning ($F_{(1, 28)} = 13.23$, $p < 0.001$) at 6 months FU	3
General cognitive function												
(Peterson et al., 2002)	RCT	Single	13 (13/0); 45.0 (4.04)	13 (13/1); 48.43 (7.43)	AUD[a] (abstinent)	15 sessions (1 h) cognitive training	2 groups: 1 No intervention 2 Audio book placebo task	No, post treatment	WAIS, WMS; TMTA and B; ANAM. BDI	No significant in any outcome		1
(Rupp, 2012)	RCT	Single	20 (11/9); 45.2 (10.5)	21 (15/6); 45.5 (8.8)	AD + CI[a]	12 sessions (45–60')/4 weeks. 62 tasks with increasing difficulty	No cognitive training	No, post treatment at 4 weeks	Wide Cognitive Battery	Improved alertness ($F = 3.227$; $p = 0.05$), divided attention ($F = 4.205$, $p = 0.049$), WM ($F = 4.347$, $p = 0.044$)*, Long-term recall ($F = 4.705$,	Decreased psychological distress ($F = 6.231$, $p = 0.017$), number of symptoms ($F = 4.564$, $p = .040$), compulsion (craving) ($F = 4.125$, $p = 0.050$)	2

										$p = 0.037$), MMSE ($F = 5.770$, $p = 0.022$), CFT copy ($F = 4.425$, $p = 0.043$)		
(Gamito et al., 2014)	RCT	No	26 (19/7); 45.50 (10.18)	28 (26/2); 45.25 (10.26)	AD[a] (abstinent)	Therapist-assisted 2–3 days/week, 4 weeks. Focusing on executive function	Treatment as usual, no cognitive training	No, post treatment	MMSE; FAB; WCST; CTT	Improvement in FAB [$F_{(1,52)} = 8.00$, $p = 0.01$]	No other significant effects	3
(Oliveira et al., 2015)	Open-label	No	64[c]	105	AD[a] (abstinent) age: 47 (9.04) 79.8% men	10 sessions with exercises in the form of serious games + general treatment	General treatment	No, post treatment	MMSE; FAB; IGT; TPT; Go-no Go; conflicting instructions	WCST number of correct responses* (cognitive flexibility) [$F_{(1144)} = 5.022$; $p = 0.027$]	No other significant effects	0
Procedural learning												
(Swinnen et al., 2005)	No-RCT	No	11(10/1); 50 (5.09)	11; 49.2 (6.15)	WK (abstinent) *v.* healthy controls	Motor ability under different feedback (FB) conditions	Same as WK group	1 week	None. Absolute error in the task	Absolute error smaller in CG [$F_{(1,20)} = 14.49$, $p < 0.01$] Error scores smaller in augmented FB condition [$F_{(2,40)} = 24.54$, $p < 0.01$]		0
Errorless learning *v.* trial and error learning												
(Kessels et al., 2007)	Counter balanced self-controlled cases series	No	10 (7/3); 56.8 (8.9)		AAD + WK (without alcohol dementia, abstinent)	Learned a route in four sessions using an errorless approach	Learned a route in 4 sessions using trial-and-error approach	Post treatment	Error rate; RBMT (route recall test); CVLT (Dutch version).	No difference in performance during the test phase after the two trainings	Better explicit memory was related to a larger trial and error advantage (Spearman $\rho = 0.63$)*	2
(Oudman et al., 2013)	Open-label	No	8 (7/1); 58.9 (6.9)	8 (7/1); 58.9 (7.2)	AAD + WK[a] (abstinent)	Learning of a task with an errorless learning approach	Learning of a task using a trial-and-error approach	4 weeks	Scale ad hoc; RAVLT; digit span; Action Programme test	Similar improvement in the two groups	Spatial lay-out improvement in the EG ($F_{(1, 7)} = 7.0$, MMSE = 9.9, $p = 0.03$)*	1
(Rensen et al., 2017)	No-RCT	No	51 (38/13); 59.9 (6.3)	31 (22/9); 62.2 (8.1)	WK[a] (abstinent)	Errorless training to relearn 2 instrumental tasks	Treatment as usual	14 months after baseline and 5 after training	MoCA	Successfully learned the tasks, i.e personal hygiene ($Z = -2.11$, $p = 0.035$)	Higher scores in quality of life ‘ ($Z = -2.30$, $p = 0.022$)	0

(*Continued*)

Table 1. (*Continued.*)

Ref.	Design	Double blind	EG (M/F); age mean (SD)	CG (M/F); age mean (SD)	Diagnose	Intervention	Control intervention	Follow-up	Neuropsychological instrument	Main outcome	Secondary outcome	Jadad (0–5)
Component method												
(Goldman and Goldman, 1988)	RCT	No	100% male group 1: 31.14 (5.47) Group 2: 31.77 (4.34)	100% male group 3: 33.07 (4.48) Group 4: 31.6 (5.09) Healthy controls: 34.15 (3.18)	AD ($n = 53$) (abstinent) *v.* non-alcoholic ($n = 13$)[a]	2 sessions of visuospatial processing training on days 10–11 (group 1) or 18–19 (group 2) of a 1 month treatment	No cognitive remediation. Assessed at day 10–11 (group 3) or 18–19 (group 4). Healthy controls day 19	No, post treatment	TMTB; WAIS-R vocabulary; BDI	Group 1 better performance in Digit symbol ($F = 12.8$)** than group 2. No other significant differences.	Comparison between non-remediated and healthy controls ($t = -2.92, 61$)**, so little recovery in the absence of remediation	2
(Gunn et al., 2018)	RCT	Not reported	75 (41/34); 22.08 (2.22) $n = 35$ AUD $n = 40$ no AUD	76 (26/50); 22.04 (2.63) $n = 34$ AUD $n = 36$ no AUD	AUD	Active training (AT): OS and SS. 15 sessions: each training 8 sets of 3 trials. Session started in the level achieved in the previous one	Visual search training difficulty was adapted to performance	4 and 30 days	Near transfer tasks: RTS, RDS, ACT. Moderate transfer: RLS, RSS, KT	AT superior in RTS [−7.79 (−12.37, −3.20), $p < 0.001$]** and ACT [−2.85 (−5.33, −0.37)]* at 4 days FU. AT superior at 30 days FU on RTS [−5.69(−10.26, −1.11)]*, ACT [−4.05 (−6.53, −1.58)]**	Baseline WM predicted greater improvement on RDS [0.34 (0.17, 0.50), $p < 0.001$] RTS [0.28 (0.14, 0.41), $p < 0.001$], KT [0.13 (0.05, 0.20)]**. Baseline IQ improvement on RTS [0.18 (0.03, 0.33)]*, ACT [0.18 (0.08, 0.28), $p < 0.001$], RLS [0.19 (0.04, 0.33)]*	2
Other interventions												
(Godfrey and Knight, 1985)	RCT	Yes	4	5	AAD ($n = 7$), AD ($n = 2$), dementia associated with alcoholism ($n = 2$), and AAD ($n = 1$). Age: 57.1 (12.5)	4 group sessions/ week for 8 weeks. Memory training conditions	4 group sessions/week for 8 weeks. No memory training activities	14th and 15th weeks after treatment	IMIS	Same improvement in both groups. Only EG improved in the orientation task [$F_{(3, 27)} = 6.16$, $p < 0.01$]	EG and CG improved global memory [$F_{(2, 14)} = 21.33$, $p < 0.01$] and practical task scores [$F_{(2, 14)} = 19.06$]** maintained at FU**	3

EG, experimental(training) group; CG, control group; RCT, randomised controlled trial; AUD, alcohol use disorder; AD, alcohol dependence; AAD, alcohol-induced persisting amnesic disorder; CI, cognitive impairment; WM, Working Memory; CANTAB, Cambridge Neuropsychological Test Automated Battery; WMS, Wechsler Memory Scale; DD task, Delay Discounting Rate; EFT, Episodic Future Thinking; HVLT, Hopkins Verbal Learning Test Revised; WAIS(-r), Wechsler Adult Intelligence Scale (-revised); TMT, Trail Making Test; ANAM, Automated Neuropsychological Assessment Metrics; BDI, Beck Depression Inventory; MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; WCST, Wisconsin Card Sorting Test; CTT, Color Trail Test; IGT, Iowa Gambling Task; TPT, Toulouse Pieron Test; RBMT, The Rivermead Behavioural Memory Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; MoCA, Montreal Cognitive Assessment; RTS, Rotation Span; RDS, Reading Span; ACT, Auditory Consonant Trigram; RLS, Running Letter Span; RSS, Running Spatial task; KT, Keep track Task; IMIS, Memory-focused neuropsychological assessment battery including Inpatient Memory Impairment.*$p < 0.05$; **$p < 0.01$;.

[a]Presence of an additional psychological and/or medical disorder as an exclusion criterion.

[b]Untreated psychological comorbid disorder as an exclusion criterion.

[c]Sample size calculation is specified.

Table 2. Pharmacological interventions for alcohol-related cognitive impairment

Ref.	Design	Double blind	EG (M/F); age mean (SD)	CG (M/F); age mean (SD)	Diagnose	Cognitive domain	Intervention	Control intervention	Follow-up	Neuropsychological instrument	Main outcome	Secondary outcome	Jadad (0–5)
B complex vitamins: Thiamine													
(Ambrose et al., 2001)	RCT	Yes	18; 39.80 (9.66)	5 mg (n = 20); 42.1 (10.80) 20 mg (n = 24); 43.67 (11.46) 50 mg (n = 21); 42.82 (12.56) 100 mg (n = 24); 39.93 (10.30)	AD without the triad of acute symptoms associated with WKS (abstinent)	Working memory	200 mg/day	5, 20, 50, 100 mg/day	No. Post treatment	Delayed alternation (DA) task	Superior performance of the EG on the DA task [t(104) = 2.18, p = 0.031]		3
Antidepressants													
Fluvoxamine													
(Martin, 1989)	RCT cross-over	Yes	10 (9/1). Amnestic n = 6; 66±2, dementia n = 3; 60±5. Alcoholic liver disease n = 1; 62		Alcoholic organic brain disease[a] abstinent	Episodic memory	200 mg/day	Placebo	No. Post treatment	WMSMQ, clinical assessment of memory function, vigilance, free recall, and recognition	Increased number of words recalled after 1' distracting task**	Increase in global memory function WMSMQ*	3
(O'Carroll et al., 1994)	RCT cross-over	Yes	8(5/3); 69.3 (4.1)		WK[a]	Global cognitive function	200 mg/day 4 weeks	Placebo	No. Post treatment	Wide memory assessment + mood change scale	No cognitive enhancement. Rivastigmine impaired verbal fluency*	Depressive symptoms after rivastigmine in 2 patients	4
(Martin et al., 1995)	RCT cross-over	Yes	10 (9/1); 63 (10)		Alcohol amnestic disorder[a] (abstinent)	Global cognitive function	100–600 mg/day 6 weeks	Placebo 3 weeks	No. Post treatment	WAIS; WMS; WCST	No improvement in WMSMQ	No changes in other functions	3
Reboxetine													
(Reuster et al., 2003)	Non-RCT	Not blind	105 (80/25); 49.8	105. Matched to EG.	WK[a] abstinent	Global mental state	8 mg/day (2-4 mg doses) 4 weeks	No reboxetine	No. Post treatment	MMSE	No beneficial effects on cognition		1
Acetylcholinesterase inhibitors: Rivastigmine													
(Djokic and Zivkovic, 2009)	Open label	No	No data	No data	101 AIPD patients	Global cognitive function	3–12 mg/day rivastigmine 4 weeks	Treatment as usual	3 months	MMSE, BPRS, CGI1-4, clock drawing test (CDT)	Effect on MMSE, BPRS, CGI1 the 28th treatment day. Higher improvement months 2&3		0

(*Continued*)

Table 2. (*Continued.*)

Ref.	Design	Double blind	EG (M/F); age mean (SD)	CG (M/F); age mean (SD)	Diagnose	Cognitive domain	Intervention	Control intervention	Follow-up	Neuropsychological instrument	Main outcome	Secondary outcome	Jadad (0–5)
(Luykx et al., 2008)	Non- RCT	No	5 (5/0); 46.2 (7.67)	5(5/0); 47.4 (3.97)	WK (abstinent)	Memory	1.5 mg/12 h in weeks 1&2;3 mg/12 h in weeks 3&4;4.5 mg/12hin weeks 5&6; 6 mg/ 12 h week 7–6 months	Treatment as usual 6 months	No. Post treatment	Word image learning test, verbal fluency test, a verbal memory test, AVLT	No differences between groups		1
Clonidine													
(Mair and McEntee, 1986)	RCT cross-over	Yes	8 (1 drop out)		Korsakoff psychosis	Memory, attention, perception, digit symbol substitution	0.2 mg clonidine	25 mg Ephedrine, 100 mg L-dopa with 10 mg carbodopa		WMS, Randt Memory Scale	No effects on cognition	Significant contrasts for Clonidine-placebo and L-dopa-placebo In Stroop	3
(O'Carroll et al., 1993)	RCT cross-over	Yes	18 (12/6); 65.8 (5.4)		WK[a]	Global cognitive function	0–3 mg twice daily. Two weeks	Placebo	No. post treatment	Wide Test Battery	No effects on cognition	No effects on other measures	2
Desglycinamide-arginine-vasopressin													
(Laczi et al., 1983)	RCT	Yes	6(4/2); 55.7 (50.65)	8(7/1); 53.5 (48.61)	WK[a]		80 μg DGAVP daily, divided into 2 portions for 7 day	Placebo daily divided into 2 portions for 7 day	2 weeks	Wide Test Battery	No differences between groups		4
Memantine													
(Rustembegović et al., 2003)	RCT	No	16 (8/8); 62 (5.8)	16 (8/8); 63 (6.1)	WK	Global cognitive function	10 mg/12 h for 28 weeks	Not specified	No. At 2, 4,8 week study	MMSE, CGI-I, ADCS-ADL	Improvement in MMSE**	Improved CGI-I	0
Metylphenidate													
(O'Donnell et al., 1986)	RCT cross-over	Yes	6(6/0); 55.67 years		Alcohol amnestic disorder[a]	Short and long term memory	3 weeks administration	1 week oral placebo		Memory for digit sequences, list-learning task	Effect on long term memory*		3

EG, experimental(training) group; CG, control group; RCT, randomised controlled trial; WK, Wernicke–Korsakoff; AD, alcohol dependence; WMSMQ, Wechsler Memory Scale Memory Quotient; WMS, Wechsler Memory Scale; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; MMSE, Mini Mental State Examination; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression Category; AVLT, Rey Auditory Verbal Learning Test; ADCS-ADL, Alzheimer's Disease Cooperative Study Group-Activities of Daily Living Scale; DGAVP, desglycinamide-arginine-vasopressin.*$p < 0.05$; **$p < 0.01$.

[a]Presence of an additional psychological and/or medical disorder as an exclusion criterion.

Table 3. Summary of the interventions: quality of the studies and effect size

Intervention	Quality of the study (Jadad Scale)	Effect size
Cognitive interventions		
Technology-based interventions		
COGMED® (Khemiri et al., 2019)	Jadad Scale: 4	Partial $\eta^2 = 0.142$. Medium effects
COGMED® (Snider et al., 2018)	Jadad Scale: 3	$r^2 = 0.15$. Small effects
Posit Science software® (Bell et al., 2016)	Jadad Scale: 3	Cohen's D from 1.01 to 1.31. Large effects
Computer-based programme (Peterson et al., 2002)	Jadad Scale: 1	Unable to calculate due to the lack of differences between the experimental and control group
Computer-based intervention (Rupp, 2012)	Jadad Scale: 2	η^2 values around 0.1 for cognitive outcomes. Moderate effects η^2 values from 0.1 to 0.15 for secondary outcomes. Moderate effects
Serious Game (Gamito et al., 2014)	Jadad Scale: 3	$\eta^2 = 0.16$. Large effects
Serious Game (Oliveira et al., 2015)	Jadad Scale: 0	Cohen's $D = 0.026$. Small effects
Procedural learning (Swinnen et al., 2005)	Jadad Scale: 0	Cohen's $D = -0.65$. Medium effects
Errorless learning		
(Kessels et al., 2007)	Jadad Scale: 2	Unable to calculate due to the lack of differences between the experimental and control group
(Oudman et al., 2013)	Jadad Scale: 0	$\eta^2 = 0.5$. Large effects
(Rensen et al., 2017)	Jadad Scale: 0	Unable to calculate due to lack of data
Component method (Goldman and Goldman, 1988)	Jadad Scale: 2	$r^2 = 0.37$. Medium effects
Component method (Gunn et al., 2018)	Jadad Scale: 2	Cohen's $D = 0.35$. Small effects
Rehabilitation programme (Godfrey and Knight, 1985)	Jadad Scale: 3	Unable to calculate due to lack of data
Pharmacological interventions		
Complex B vitamins – Thiamine (Ambrose et al., 2001)	Jadad Scale: 3	Cohen's $D = 0.22$. Small effect
Antidepressants		
Fluvoxamine (Martin, 1989)	Jadad Scale: 3	Unable to calculate due to the lack of differences between the experimental and control group
Fluvoxamine (O'Carroll et al., 1994)	Jadad Scale: 4	Unable to calculate due to lack of data
Fluvoxamine (Martin et al., 1995)	Jadad Scale: 3	Unable to calculate due to the lack of differences between the experimental and control group
Reboxetine (Reuster et al., 2003)	Jadad Scale: 1	Unable to calculate due to the lack of differences between the experimental and control group
Acetylcholinesterase inhibitor – Rivastigmine		
(Djokic and Zivkovic, 2009)	Jadad Scale: 0	Unable to calculate due to the lack of differences between the experimental and control group
(Luykx et al., 2008)	Jadad Scale: 1	Unable to calculate due to the lack of differences between the experimental and control group
Clonidine		
(Mair and McEntee, 1986)	Jadad Scale: 3	Unable to calculate due to the lack of differences between the experimental and control group
(O'Carroll et al., 1993)	Jadad Scale: 2	Unable to calculate due to the lack of differences between the experimental and control group
Desglycinamide-arginine-vasopressin (Laczi et al., 1983)	Jadad Scale: 4	Unable to calculate due to the lack of differences between the experimental and control group
Memantine (Rustembegović et al., 2003)	Jadad Scale: 0	Unable to calculate due to lack of data
Methylphenidate (O'Donnell et al., 1986)	Jadad Scale: 3	Unable to calculate due to lack of data

Interpretation of the effect size values (Cohen, 1988; Sullivan & Feinn, 2012).
Cohen's D: Cohen's $D = 0$–0.20 very small effect size; 0.2–0.5 small effect size; 0.5–0.8 medium effect size; >0.8 large effect size.
η^2: 0.01 low effect size; 0.06 medium effect size; >0.14 large effect size.
Partial η^2: 0.02 low effect size; 0.13 medium effect size; 0.26 large effect size.
r^2: 0.04 small effect size; 0.25 medium effect size; 0.64 large effect size.

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

5.73 in the control group; Swedish SDUs, 1 Standard Drink Unit = 12 g) (Khemiri et al., 2019).

Verbal learning and verbal memory: One study assessed the effect of a computerised training tool (Posit Science software®) for the enhancement of verbal learning and memory (Bell, Vissicchio, & Weinstein, 2016). The tool is designed to improve several cognitive functions including attention, memory and sensory processing through visual and auditory tasks that progress from elementary to more complex and demanding games. The sample consisted of 31 patients with alcohol use disorder that were in their first 30 days of sobriety and were receiving outpatient treatment. Severity of the diagnoses was not specified. The participants were mainly male (97%) in their 50s. Patients ($n = 15$) that practiced 5 h a week for 13 weeks presented a statistically significant increase in verbal learning and verbal memory at 3 months follow-up in comparison to the patients that received work therapy only (Cohen's D 1.01 for verbal memory and 1.09 for verbal learning). Although these effects tended to diminish, condition effects remained statistically significant at 6 months follow-up for both verbal learning and verbal memory, with Cohen's $D = 1.31$ and 1.18, respectively.

General cognitive function: Four studies found mixed results regarding the effect of technology-oriented interventions for the improvement of general cognitive function (Gamito et al., 2014; Oliveira et al., 2015; Peterson, Patterson, Pillman, & Battista, 2002; Rupp, 2012). On the one hand, a 15 one-hour sessions' programme was not significantly effective to speed up the cognitive recovery process in a group of seven recently detoxified male inpatients (mean age = 45 years) in comparison to two matched control groups (a placebo task and no treatment) (Peterson et al., 2002). On the other hand, after a 12 sessions programme consisting of 62 computerised exercises, a group of 20 patients (55% male, mean age = 45.2 years) with alcohol dependence and at least a mild cognitive impairment that were entering inpatient treatment, presented statistically significant improvements in several attention/executive functions measures: alertness, divided attention, digit-span backward; working memory measures; some memory outcomes: digit-span forward, memory long delay recall; Mini Mental State Examination (MMSE) Scores and Complex Figure Test (CFT) copy. These results presented η^2 values of about 0.1. Furthermore, the cognitive remediation intervention was related to a statistically significant decrease in psychological distress, the number of psychological symptoms and compulsive behaviour associated with craving (Rupp, 2012). These secondary results presented partial η^2 between 0.1 and 0.15.

Serious games are games that aim to produce changes in patients' health, cognition, physical activity or wellbeing, among others (Mccallum, 2012). A cognitive stimulation treatment delivered through a mobile phone serious game was designed to train memory, attention, decision making, language and processing speed in patients with alcohol dependence that were undergoing an abstinence treatment in a therapeutic community (Gamito et al., 2014; Oliveira et al., 2015). When an intervention using this tool was added to the general treatment for alcohol dependence and compared to the group that only received treatment as usual, an improvement in cognitive ability from pre-to-post treatment was observed irrespective of the group. However, statistically significant improvements in the Frontal Assessment Battery scores were shown in the experimental group ($\eta^2 = 0.16$) (Gamito et al., 2014) as well as a statistically significant higher improvement in cognitive flexibility as indicated by an increase in the number of correct responses in the Wisconsin Card Sorting Test (Oliveira et al., 2015). This improvement presented a Cohen's $D = 0.026$.

Procedural learning: One study (Swinnen, Puttemans, & Lamote, 2005) explored the acquisition of a manual coordination task in a group of 11 patients with Korsakoff Syndrome, under different conditions of feedback information (external feedback in the form of information in the computer screen; normal vision with the lack of this information in the screen; or blindfolded condition) in comparison to 11 matched healthy controls. The participants were abstinent during the study period, 90% were male and the mean age was 50 years old. Results highlight a lower performance in the acquisition and retaining of the task in the KS group when compared to healthy controls. Augmented feedback allowed for a higher coordination performance in the KS group, whereas no learning was achieved 1 week after the training in the absence of feedback (normal vision or blindfolded condition) (Cohen's $D = -0.65$).

Errorless learning v. trial and error learning

Three studies assessed the efficacy of errorless learning and trial and error learning in patients with alcohol-induced persisting amnesic disorder (Kessels, Van Loon, & Wester, 2007; Oudman et al., 2013; Rensen et al., 2017). Errorless learning refers to a learning approach that consists of preventing learners from making mistakes by using feed-forward instructions (verbal cues that guide the actions of the learner) (Oudman et al., 2013), breaking down the task in smaller steps and modelling them (Rensen, Egger, Westhoff, Walvoort, & Kessels, 2019).

The same improvement in procedural learning was found irrespective of the learning condition (Kessels et al., 2007; Oudman et al., 2013). Nonetheless, 4 weeks after the practice concluded, the performance was still high in the errorless learning condition (eight inpatients with alcoholic amnesia disorder, 88% male, mean age = 58.9 years old), while for the trial and error condition (eight matched patients), it remained similar to baseline ($\eta^2 = 0.5$) (Oudman et al., 2013). Furthermore, it was suggested that a better explicit memory function relates to a larger-trial-and-error advantage in a group of 10 inpatients with Wernicke–Korsakoff (70% male with a mean age of 56.8 years old) (Kessels et al., 2007).

Errorless learning was found to be useful to relearn daily activities in 51 inpatients with Korsakoff Syndrome (75% male, mean age = 60) in comparison to treatment as usual (Rensen et al., 2017). After errorless training, affective, psychotic symptoms as well as agitation and aggression were statistically significantly improved (Rensen et al., 2019), along with the patients' quality of life (Rensen et al., 2017).

Component method

Two studies specifically explored a component method to improve visuospatial problem-solving skills (Goldman & Goldman, 1988) and working memory (Gunn, Gerst, Wiemers, Redick, & Finn, 2018). This strategy consists of splitting complex tasks into more simple components that are learned gradually and eventually combined into the complex task. This method is indirectly included in many of the studies that are being reviewed as one of the main goals of rehabilitation interventions is to allow the transfer of the learning achieved during the learning to daily and more complex tasks.

There is a minimal improvement for visuospatial skills during the first month of abstinence in the absence of specific training (Goldman & Goldman, 1988). Training of specific task components allowed a group of male patients with alcohol use disorder

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

receiving inpatient treatment to reacquire more generalised and complex abilities. Nevertheless, authors state that there was a large variability among the results, as the group with the longer abstinence period benefitted less from this method ($r^2 = 0.37$) (Goldman & Goldman, 1988). A working memory programme (Gunn et al., 2018) positively improved several working memory transfer measures in patients with moderate-to-severe alcohol use disorder. This improvement was maintained at 30-day follow-up. A greater improvement was found for patients with higher baseline working memory and intellectual quotient levels (Cohen's $D = 0.35$) (Gunn et al., 2018).

Other interventions

A programme to enhance memory capacities was designed, which included several stimulation strategies: associate-learning tasks, reality orientation training activities, visual recognition and recall of recent events (Godfrey & Knight, 1985). When applied to nine patients with alcohol-related memory impairment (mean age = 57.9 years) who attended four 60 min group sessions per week for 8 weeks, it was found that patients from the control group ($n = 5$) increased their performance to the same level as the experimental group ($n = 4$) that had received specific training to improve memory skills. This improvement was maintained at 1 month follow-up for the total memory score and the practical task score. The only difference between groups was found for the orientation test, in which patients in the training group outperformed the controls. The effect size of these results could not be calculated due to lack of data in the article.

Pharmacological interventions

We cluster in four groups (antidepressants, B-complex vitamins, acetylcholinesterase inhibitor and other pharmacological treatment) the pharmacological interventions reviewed (Table 2).

B-complex vitamins

Only one double-blind randomised controlled trial (Ambrose, Bowden, & Whelan, 2001) exploring the effects of thiamine administration on working memory fulfilled all inclusion criteria. The administration of 200 mg/day of intramuscular thiamine to 18 patients (mean age 39.8 years) that were detoxifying from alcohol represented a statistically significant improvement in working memory (assessed by the number of trials needed to reach the learning criterion in the delayed alternation task) in comparison to lower thiamine dosages (5–100 mg/day) (Cohen's $D = 0.22$).

Antidepressants

Fluvoxamine effects on cognitive enhancement were assessed in three of the identified papers (Martin, 1989; Martin et al., 1995; O'Carroll, Moffoot, Ebmeier, & Goodwin, 1994). This serotonin reuptake inhibitor was not found to have a positive influence on cognitive enhancement in comparison to placebo. Only a double-blind placebo-controlled crossover study (Martin, 1989) found the administration of 200 mg fluvoxamine to improve episodic memory but no other cognitive areas in six patients with Korsakoff Syndrome. These results could not be replicated in further studies (Martin et al., 1995; O'Carroll et al., 1994) as they did not find statistically significant differences between placebo and the administration of 200 mg of fluvoxamine (O'Carroll et al., 1994), neither when the plasma fluvoxamine concentration was maintained at 400 ng/ml (administering fluvoxamine dosages ranging from 100 to 600 mg/day) (Martin et al., 1995).

Furthermore, impaired verbal fluency performance was found in eight patients with Korsakoff Syndrome after 4 weeks of 200 mg of fluvoxamine intake and two of the patients developed depressive symptoms that reverted to normal within 3 days of cessation of treatment (O'Carroll et al., 1994). The sample in this study consisted of five men and three women with a mean age of 69.3 years old.

In a group of 105 patients with Wernicke–Korsakoff (76% male, mean age = 49.8), 8 mg a day of reboxetine for 4 weeks (Reuster, Buechler, Winiecki, & Oehler, 2003) was not found to have a positive effect on the global cognitive function in comparison to the control group, excepting for the patients with less than a year of progression of the disease, which cognitive function (assessed with the MMSE) was statistically significantly improved. Patients did not use alcohol during the study period.

Acetylcholinesterase inhibitor

Two articles described the use of acetylcholinesterase inhibitors, specifically rivastigmine (Djokic & Zivkovic, 2009; Luykx et al., 2008), for the treatment of alcohol-induced persisting dementia (Djokic & Zivkovic, 2009) and Wernicke–Korsakoff Syndrome (Luykx et al., 2008).

Treatment with rivastigmine (3–12 mg/24 h) enhanced general cognitive and clinical measures in a group of 101 patients with alcohol-induced persisting dementia after 2 and 3 months of treatment in comparison to the control group that received only conventional treatment. However, these improvements did not reach statistical significance (Djokic & Zivkovic, 2009). In five male patients with a mean age of 46 years old presenting Wernicke–Korsakoff Syndrome that were abstinent for at least 2 months, no statistically significant differences in pre-to-post treatment changes on the memory scales were found in comparison to the control group after 6 months of treatment (Luykx et al., 2008).

Other pharmacological treatments

Neither clonidine (Mair & McEntee, 1986; O'Carroll, Moffoot, Ebmeier, Murray, & Goodwin, 1993) or desglycinamide-arginine-vasopressin (Laczi et al., 1983) were found to have a positive effect on global cognitive function (O'Carroll et al., 1993), memory, attention and perception (Mair & McEntee, 1986) in patients with Wernicke–Korsakoff.

Memantine intake improved global cognitive function in 16 patients with moderately severe dementia (50% male, mean age = 62 years) with Wernicke–Korsakoff Syndrome (Rustembegović, Kundurović, Sapcanin, & Sofic, 2003). However, statistical data were not provided in the article.

The effects of the psychostimulant methylphenidate on short- and long-term memory were explored in a double-blind crossover study with six male patients aged 55–67, suffering from alcohol amnestic disorder (O'Donnell, Pitts, & Fann, 1986). Statistically significant improvement in long-term memory was found after 3 weeks of treatment.

Quality of the studies (Jadad Scale)

In this section, results regarding the quality of the studies included in the present review, as measured with the Jadad Scale, will be presented (Table 3). As explained in the Methods section, the anchors of the scale range from 0 to a maximum of 5, depending on how the randomisation and blinding have been conducted and whether the information is presented in the

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

article, and also depending on if the fate of all the participants in the study has been specified.

The quality of the studies assessing the efficacy of neuropsychological treatments is moderate for most of them, as only one scored 4, four studies scored 3, four scored 2, two scored 1 and three scored 0. The study with the higher quality score indicated the effectivity of a technology-based intervention (COGMED®) to improve verbal working memory in patients with alcohol use disorder initiating treatment. These results presented a large effect size ($\eta^2 = 0.142$) (Khemiri et al., 2019).

Regarding the quality of the 12 studies on pharmacological interventions, more than half presented a good or moderate quality in the Jadad Scale (Jadad score 4 for fluvoxamine and desglycinamide-arginine-vasopressin; Jadad score 3, for thiamine, two studies on fluvoxamine, clonidine, methylphenidate). None obtained the maximum score in the Jadad Scale, one scored 2 (clonidine), two scored 1 (reboxetine and rivastigmine) and one scored 0 (rivastigmine). The two studies with higher quality scores studied fluvoxamine and desglycinamide-arginine-vasopressin, which were not found to be better than placebo to improve cognitive functions in patients with Wernicke–Korsakoff Syndrome.

Discussion

The present review was aimed at the investigation of the neuropsychological and pharmacological interventions that have been studied to improve cognitive impairment related to alcohol use.

The review revealed some strategies and interventions that had a positive effect on neuropsychological deficits. However, several concerns regarding the design of the studies included need to be considered as they interfere with the generalisation of the results to the clinical practise. Out of the 26 articles included for revision, a half ($n = 12$) had a sample size smaller than 30 individuals and only four included at least 100 individuals. Sample size calculation was performed in only one of the studies. Among the neuropsychological treatments, only two (14.29%) were double blinded and eight (66.66%) in the pharmacological group. It is also important to consider that from the 24 studies that reported the sample sociodemographic data, 11 had performed the training in groups with mean ages lower than 50 ($n = 8$, 57.14% of the neuropsychological interventions; $n = 3$, 30% of the pharmacological). Furthermore, three of the neuropsychological studies had mean ages lower than 40. When deploying these interventions to samples with older ages, performance could be lower, as besides the impairment related to alcohol use, it may coexist a deterioration in brain structures due to ageing (Hayes et al., 2016); therefore, age is a confounding factor that should be controlled in further studies. Finally, in some of the studies, the diagnosis of the included sample is not sufficiently specified (for instance, the severity of the alcohol use disorder). Thus, a greater characterisation of the sample would help to a more accurate interpretation of the results.

Results from the present review show that cognitive interventions can be successfully performed through technological devices, as computer-based interventions were found to effectively improve working memory function (Khemiri et al., 2019; Snider et al., 2018), verbal learning and verbal memory (Bell et al., 2016), several attention and executive functions, memory, and MMSE scores (Rupp, 2012), functions associated with frontal lobes (Gamito et al., 2014), and cognitive flexibility (Oliveira et al., 2015). In some studies in which abstinence was not required, these improvements were accompanied by secondary positive changes in behavioural responses such as the reduction in alcohol consumption (Khemiri et al., 2019), and a decrease in psychological distress, the number of psychological symptoms and compulsive behaviour associated with craving (Rupp, 2012).

Digital tools allow a flexible deployment of tasks directed to specific needs adapting the difficulty level to the patients' performance. However, for most of the interventions reviewed, the training mirrored traditional interventions based on the repetition of exercises that do not resemble daily life activities, which may hinder the transferring and generalisation of the acquired abilities into the natural environment. Thus, digital tools present some distinct characteristics that can serve as a solution to this limitation by allowing the development of exercises and virtual scenarios that involve daily life activities which can potentially increase the generalisation of the outcomes trained (Rochat & Khazaal, 2019; Tuena et al., 2019). For instance, through virtual reality, patients can interact with relevant stimuli in familiar contexts that demand real-world functional behaviours (Lange et al., 2010). Also, the characteristics of serious games (e.g. interactive, offer feedback, appealing to the eye) make them motivating for the patients (Oliveira et al., 2017). Lastly, these solutions, such as mobile-based interventions, have been suggested to be cost-effective (Soler González et al., 2014), as they can be administered with minimum or even without supervision (Cameirao, Bermudez i Badia, Duarte Oller, & Verschure, 2010) and improve accessibility to treatment in people that would be traditionally excluded (Gamito et al., 2017).

Several techniques other than computerised interventions have been used to cope with cognitive impairments in ARCI. For instance, errorless learning was found to be a useful approach to learn (or relearn) skills (Kessels et al., 2007; Oudman et al., 2013; Rensen et al., 2017) as well as splitting the learning material into simpler components that are learned gradually (Goldman & Goldman, 1988; Gunn et al., 2018) and adding external feedback when teaching new procedures (Swinnen et al., 2005).

There are other rehabilitation interventions or specific strategies that did not fulfil inclusion criteria for the present review, that have also shown promising results for the rehabilitation of cognitive deficits in patients with ARCI, such as future event simulation to improve prospective memory (Platt, Kamboj, Italiano, Rendell, & Curran, 2016), mnemonic strategies like 'chunking' to enhance working memory performance (Haj, Kessels, Urso, & Nandrino, 2018) or the use of salient cues to improve prospective memory (Altgassen, Ariese, Wester, & Kessels, 2016). However, these strategies have not been evaluated in prospective controlled trials but could be considered in future studies.

Regarding the pharmacological interventions, among the treatments reviewed, three (thiamine, memantine and methylphenidate) produced a statistical significance cognitive improvement. The improvement in WK after 200 mg/day of thiamine is still preliminary due to the small sample size in each group and the short duration of the treatment (Ambrose et al., 2001). There is still insufficient data regarding dosage and duration of the treatment with thiamine (Day, Bentham, Callaghan, Kuruvilla, & George, 2013), however intervention with b-vitamins could help prevent dementia development or progression in patients with AUD (Chou et al., 2018). The effect of methylphenidate on cognition was assessed in a single cross-over study with a small sample size ($n = 6$) (O'Donnell et al., 1986). On the other hand, evidence regarding the effect of the N-methyl-D-aspartate, memantine (Rustembegović et al., 2003) on cognitive functions is weak, as

https://doi.org/10.1017/S0033291720002925 Published online by Cambridge University Press

information about the methodology and specific data obtained was lacking in the article, and no replication of these effects has been found. The quality of the evidence of these studies, assessed with the Jadad Scale, is moderate (3) for thiamine and methylphenidate, and low (0) for memantine.

The present review reveals an important heterogeneity among the cognitive domains in which the interventions focus on, as well as among the interventions themselves. One of the explanations for this heterogeneity could be the fact that ARCI encompasses a spectrum of disorders (Bates et al., 2002; Hayes et al., 2016) in which cognitive impairments differ largely between patients, depending on the brain structures affected and the severity of the impairment. Also, it is needed to build consensus on the cognitive domains in which rehabilitation interventions should focus on, in order to produce, in turn, a higher impact on the management of addiction and psychological wellbeing. Strengthening memory and executive functioning should be preferent targets due to its influence in treatment outcome and abstinence maintenance by enhancing positive behavioural outcomes (Bates et al., 2013; Bernardin et al., 2014; Brion et al., 2017; Houben, Wiers, & Jansen, 2011). Lastly, more research is needed to clarify the association between the reduction of alcohol use and cognitive improvements in patients with alcohol use disorder, as the weight of each factor in the interaction has not been studied yet.

Although the extracted results give an in-depth analysis of how cognitive impairments in ARCI are being addressed and the need of developing ecological training to improve them, some limitations of the present review have to be taken into account. First, the number of articles (14 for neuropsychological and 12 for pharmacological interventions) included in the current revision is relatively low, because of the strict inclusion criteria we established to guarantee a minimum quality. Despite these efforts, some of the articles analysed have limitations that prevent us from extracting robust conclusions about the efficacy of the interventions. As stated earlier, sample sizes of the included studies are small and, in most of them, sample size calculations have not been conducted. Also, it was not possible to carry out a meta-analysis due to the heterogeneity of the studies. Lastly, the generalisation of the results is also hindered by the lack of replication of the studies. Despite these limitations, we have applied strong measures in order to guarantee the quality of the included studies, as data were extracted following the PRISMA guidelines, only longitudinal studies have been considered, and the quality of these studies has been assessed using the Jadad Scale.

Conclusions

Results point out how cognitive functions can be improved by using specific neuropsychological and pharmacological interventions. In some studies, these cognitive improvements happened at the same time as alcohol use reduction; however, the impact of one factor on the other is not clear and needs more research. However, methodological weaknesses of studies in this field prevent from having a gold standard treatment for ARCI. Randomised clinical controlled trials with large sample sizes are required as well as interventions that ease the transference of the acquired abilities to daily life. Considering the cost-effectiveness of digital interventions, and their promising role for the development of ecological treatments, they should be considered in future studies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002925.

Author contributions.
Conceptualization: EC and HL-P; methodology: EC, HL-P, CO, LN; writing – original draft preparation: EC, HL-P; writing – review and editing: EC, HL-P, CO, LN, MB, AG.

Financial support. This research received no external funding. H.L.-P. received funding from the Spanish Ministry of Science, Innovation and Universities, Instituto de Salud Carlos III through a 'Rıo Hortega' contract (CM17/00123, to Dr López-Pelayo), with the support of the European Social Fund.

Conflict of interest. H.L.-P. has received travel grants from the laboratories honoraria and travel grants from Janssen and Lundbeck; A.G has received honoraria from Lundbeck. None of these COI is related to the current research. The rest of the authors declare no conflict of interest.

References

Altgassen, M., Ariese, L., Wester, A. J., & Kessels, R. P. C. (2016). Salient cues improve prospective remembering in Korsakoff's syndrome. *British Journal of Clinical Psychology*, *55*(2), 123–136. doi:10.1111/bjc.12099.

Ambrose, M. L., Bowden, S. C., & Whelan, G. (2001). Thiamin treatment and working memory function of alcohol-dependent people: Preliminary findings. *Alcoholism: Clinical and Experimental Research*, *25*(1), 112–116. doi:10.1111/j.1530-0277.2001.tb02134.x.

Barrio, P., Teixidor López, L., Gual, A., Moreno-España, J., Frías-Torres, C., & Ortega, L. (2016). Terapia de rehabilitación cognitiva en pacientes con trastorno por consumo de alcohol y trastorno neurocognitivo. Estudio piloto. *Adicciones*, *30*, 93–100. doi:10.20882/adicciones.757.

Bates, M. E., Bowden, S. C., & Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Experimental and Clinical Psychopharmacology*, *10*(3), 193–212. doi:10.1037/1064-1297.10.3.193.

Bates, M. E., Buckman, J. F., & Nguyen, T. T. (2013). A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychology Review*, *23*(1), 27–47. doi:10.1007/s11065-013-9228-3.

Bates, M. E., Pawlak, A. P., Tonigan, J. S., & Buckman, J. F. (2006). Cognitive impairment influences drinking outcome by altering therapeutic mechanisms of change. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*, *20*(3), 241. doi:10.1037/0893-164X.20.3.241.

Bell, M. D., Vissicchio, N. A., & Weinstein, A. J. (2016). Cognitive training and work therapy for the treatment of verbal learning and memory deficits in veterans with alcohol use disorders. *Journal of Dual Diagnosis*, *12*(1), 83–89. doi:10.1080/15504263.2016.1145779.

Bernardin, F., Maheut-Bosser, A., & Paille, F. (2014). Cognitive impairments in alcohol-dependent subjects. *Frontiers in Psychiatry*, *5*(JUL), 1–6. doi:10.3389/fpsyt.2014.00078.

Blume, A. W., & Alan Marlatt, G. (2009). The role of executive cognitive functions in changing substance use: What we know and what we need to know. *Annals of Behavioral Medicine*, *37*(2), 117–125. doi:10.1007/s12160-009-9093-8.

Blume, A. W., Schmaling, K. B., & Marlatt, G. A. (2005). Memory, executive cognitive function, and readiness to change drinking behavior. *Addictive Behaviors*, *30*(2), 301–314. doi:10.1016/J.ADDBEH.2004.05.019.

Brion, M., D'Hondt, F., Pitel, A.-L., Lecomte, B., Ferauge, M., de Timary, P., … Lecomte, B. (2017). Executive functions in alcohol-dependence: A theoretically grounded and integrative exploration. *Drug and Alcohol Dependence*, *177*(February), 39–47. doi:10.1016/j.drugalcdep.2017.03.018.

Cameirao, M. S., Bermudez i Badia, S., Duarte Oller, E., & Verschure, P. F. (2010). Neurorehabilitation using the virtual reality based Rehabilitation Gaming System: Methodology, design, psychometrics, usability and validation. *Journal of NeuroEngineering and Rehabilitation*, *7*(1), 48. doi:10.1186/1743-0003-7-48.

Chou, W.P., Chang, Y.H., Lin, H.C., Chang, Y.H., Chen, Y.Y., & Ko, C.H. (2018). Thiamine for preventing dementia development among patients with alcohol use disorder: A nationwide population-based cohort study.

Clinical Nutrition (Edinburgh, Scotland), *38*(3), 1269–1273. doi:10.1016/j.clnu.2018.05.009.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillside, NJ: Lawrence Erlbaum Associates, Inc.

Czapla, M., Simon, J. J., Richter, B., Kluge, M., Friederich, H.-C., Herpertz, S., … Loeber, S. (2016). The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: Implications for psychotherapeutic treatment. *Addiction Biology*, *21*(4), 873–884. doi:10.1111/adb.12229.

Day, E., Bentham, P. W., Callaghan, R., Kuruvilla, T., & George, S. (2013). Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. *The Cochrane Database of Systematic Reviews*, *2013*(7), CD004033. doi:10.1002/14651858.CD004033.pub3.

Djokic, G., & Zivkovic, N. (2009). P01-28 Rivastigmine in treatment of alcohol-induced persisting dementia. *European Psychiatry*, *24*, S416. doi:10.1016/S0924-9338(09)70649-2.

Domínguez-Salas, S., Díaz-Batanero, C., Lozano-Rojas, O. M., & Verdejo-García, A. (2016). Impact of general cognition and executive function deficits on addiction treatment outcomes: Systematic review and discussion of neurocognitive pathways. *Neuroscience & Biobehavioral Reviews*, *71*, 772–801. doi:10.1016/J.NEUBIOREV.2016.09.030.

Florez, G., Espandian, A., Villa, R., & Saiz, P. A. (2019). Clinical implications of cognitive impairment and alcohol dependence Deterioro cognitivo y dependencia alcohólica, implicaciones clínicas. *Adicciones*, *31*(1), 3–7.

Gamito, P., Oliveira, J., Lopes, P., Brito, R., Morais, D., Caçoete, C., … Oliveira, H. (2017). Cognitive training through mHealth for individuals with substance use disorder. *Methods of Information in Medicine*, *56*(2), 156–161. doi:10.3414/me16-02-0012.

Gamito, P., Oliveira, J., Lopes, P., Brito, R., Morais, D., Silva, D., … Deus, A. (2014). Executive functioning in alcoholics following an mHealth cognitive stimulation program: Randomized controlled trial. *Journal of Medical Internet Research*, *16*(4), e102. doi:10.2196/jmir.2923.

Godfrey, H. P. D., & Knight, R. G. (1985). Cognitive rehabilitation of memory functioning in amnesiac alcoholics. *Journal of Consulting and Clinical Psychology*, *53*(4), 555–557. doi:10.1037/0022-006X.53.4.555.

Goldman, R. S., & Goldman, M. S. (1988). Experience-dependent cognitive recovery in alcoholics: A task component strategy. *Journal of Studies on Alcohol*, *49*(2), 142–148. doi:10.15288/jsa.1988.49.142.

Gunn, R. L., Gerst, K. R., Wiemers, E. A., Redick, T. S., & Finn, P. R. (2018). Predictors of effective working memory training in individuals with alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, *42*(12), 2432–2441. doi:10.1111/acer.13892.

Haj, E. M., Kessels, R., Urso, L., & Nandrino, J. L. (2018). Chunking to improve verbal forward spans in Korsakoff's syndrome. *Applied Neuropsychology: Adult*, *0*(0), 1–8. doi:10.1080/23279095.2018.1499023.

Harper, C. (2009). The neuropathology of alcohol-related brain damage. *Alcohol and Alcoholism*, *44*(2), 136–140. doi:10.1093/alcalc/agn102.

Hayes, V., Demirkol, A., Ridley, N., Withall, A., & Draper, B. (2016). Alcohol-related cognitive impairment: Current trends and future perspectives. *Neurodegenerative Disease Management*, *6*(6), 509–523. doi:10.2217/nmt-2016-0030.

Horton, L., Duffy, T., & Martin, C. (2015). Neurocognitive, psychosocial and functional status of individuals with alcohol-related brain damage (ARBD) on admission to specialist residential care. *Drugs: Education, Prevention and Policy*, *22*(5), 416–427. doi:10.3109/09687637.2015.1050997.

Horton, L., Duffy, T., & Martin, C. R. (2014). Interventions for alcohol-related brain damage (ARBD): Do specific approaches restrict the evolution of comprehensive patient care? *Drugs: Education, Prevention and Policy*, *21*(5), 408–419. doi:10.3109/09687637.2014.924481.

Houben, K., Wiers, R. W., & Jansen, A. (2011). Getting a grip on drinking behavior. *Psychological Science*, *22*(7), 968–975. doi:10.1177/0956797611412392.

Ioime, L., Guglielmo, R., Affini, G. F., Quatrale, M., Martinotti, G., Callea, A., … Janiri, L. (2018). Neuropsychological performance in alcohol dependent patients: A one-year longitudinal study. *Psychiatry Investigation*, *15*(5), 505–513. doi:10.30773/pi.2017.09.27.1.

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*, *17*(1), 1–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8721797.

Kessels, R., Van Loon, E., & Wester, A. (2007). Route learning in amnesia: A comparison of trial-and-error and errorless learning in patients with the Korsakoff syndrome. *Clinical Rehabilitation*, *21*(10), 905. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=amed&AN=0104361&site=ehost-live.

Khemiri, L., Brynte, C., Stunkel, A., Klingberg, T., & Jayaram-Lindström, N. (2019). Working memory training in alcohol use disorder: A randomized controlled trial. *Alcoholism: Clinical and Experimental Research*, *43*(1), 135–146. doi:10.1111/acer.13910.

Laczi, F., Van Ree, J. M., Balogh, L., Szász, A., Járdánházy, T., Wágner, A., … De Wied, D. (1983). Lack of effect of desglycinamide-arginine-vasopressin (DGAVP) on memory in patients with Korsakoff's syndrome. *Acta Endocrinologica*, *104*(2), 177–182. doi:10.1530/acta.0.1040177.

Lange, B. S., Requejo, P., Flynn, S. M., Rizzo, A. A., Valero-Cuevas, F. J., Baker, L., & Winstein, C. (2010). The potential of virtual reality and gaming to assist successful aging with disability. *Physical Medicine and Rehabilitation Clinics of North America*, *21*(2), 339–356. doi:10.1016/j.pmr.2009.12.007.

Luykx, H. J., Dorresteijn, L. D. A., Haffmans, P. M. J., Bonebakker, A., Kerkmeer, M., & Hendriks, V. M. (2008). Rivastigmine in Wernicke-Korsakoff's syndrome: Five patients with rivastigmine showed no more improvement than five patients without rivastigmine. *Alcohol and Alcoholism*, *43*(1), 70–72. doi:10.1093/alcalc/agm158.

Mair, R. G., & McEntee, W. J. (1986). Cognitive enhancement in Korsakoff's psychosis by clonidine: A comparison with l-Dopa and Ephedrine. *Psychopharmacology*, *88*(3), 374–380. doi:10.1007/BF00180841.

Manning, V., Verdejo-Garcia, A., & Lubman, D. I. (2017). Neurocognitive impairment in addiction and opportunities for intervention. *Current Opinion in Behavioral Sciences*, *13*, 40–45. doi:10.1016/j.cobeha.2016.10.003.

Martin, P. R. (1989). Effective pharmacotherapy of alcoholic amnestic disorder with fluvoxamine. *Archives of General Psychiatry*, *46*(7), 617. doi:10.1001/archpsyc.1989.01810070043008.

Martin, P. R., Adinoff, B., Lane, E., Stapleton, J. M., Bone, G. A. H., Weingartner, H., … Eckardt, M. J. (1995). Fluvoxamine treatment of alcoholic amnestic disorder. *European Neuropsychopharmacology*, *5*(1), 27–33. doi:10.1016/0924-977X(94)00129-Y.

Mccallum, S. (2012). Gamification and serious games for personalized health. *Studies in Health Technology and Informatics*, *177*, 85–96. 10.3233/978-1-61499-069-7-85.

Moerman-van den Brink, W. G., van Aken, L., Verschuur, E. M. L., Walvoort, S. J. W., Egger, J. I. M., & Kessels, R. P. C. (2019). Executive dysfunction in patients with Korsakoff's syndrome: A theory-driven approach. *Alcohol and Alcoholism* (*Oxford, Oxfordshire*), *54*(1), 23–29. doi:10.1093/alcalc/agy078.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. doi:10.1371/journal.pmed.1000097.

Moraleda Barreno, E., Domínguez-Salas, S., Díaz-Batanero, C., Lozano, ÓM, Lorca Marín, J. A., & Verdejo-García, A. (2019). Specific aspects of cognitive impulsivity are longitudinally associated with lower treatment retention and greater relapse in therapeutic community treatment. *Journal of Substance Abuse Treatment*, *96*, 33–38. doi:10.1016/J.JSAT.2018.10.004.

Mulhauser, K., Weinstock, J., Ruppert, P., & Benware, J. (2018). Changes in neuropsychological status during the initial phase of abstinence in alcohol use disorder: Neurocognitive impairment and implications for clinical care. *Substance Use and Misuse*, *53*(6), 881–890. doi:10.1080/10826084.2017.1408328.

O'Carroll, R. E., Moffoot, A. P. R., Ebmeier, K. P., & Goodwin, G. M. (1994). Effects of fluvoxamine treatment on cognitive functioning in the alcoholic Korsakoff syndrome. *Psychopharmacology*, *116*(1), 85–88. doi:10.1007/BF02244875.

O'Carroll, R. E., Moffoot, A., Ebmeier, K. P., Murray, C., & Goodwin, G. M. (1993). Korsakoff's syndrome, cognition and clonidine. *Psychological Medicine*, *23*(2), 341–347. doi:10.1017/S0033291700028440.

O'Donnell, V. M., Pitts, W. M., & Fann, W. E. (1986). Noradrenergic and cholinergic agents in Korsakoff's syndrome. *Clinical Neuropharmacology*, *9*(1), 65–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3548954.

Oliveira, J., Gameiro, F., Gamito, P., Morais, D., Lopes, P., Brito, R., & Bento, B. (2015). Cognitive stimulation of alcoholics through VR-based Instrumental Activities of Daily Living, 14–17. doi:10.1145/2838944.2838948.

Oscar-Berman, M., & Marinković, K. (2007). Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychology Review*, *17*(3), 239–257. doi:10.1007/s11065-007-9038-6.

Oudman, E., Nijboer, T. C. W., Postma, A., Wijnia, J. W., Kerklaan, S., Lindsen, K., & Van Der Stigchel, S. (2013). Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: A comparison of trial and error and errorless learning. *Neuropsychological Rehabilitation*, *23*(6), 888–913. doi:10.1080/09602011.2013.835738.

Peterson, M. A., Patterson, B., Pillman, B. M., & Battista, M. A. (2002). Cognitive recovery following alcohol detoxification: A computerised remediation study. *Neuropsychological Rehabilitation*, *12*(1), 63–74. doi:10.1080/09602010143000167.

Pitel, A. L., Segobin, S. H., Ritz, L., Eustache, F., & Beaunieux, H. (2015). Thalamic abnormalities are a cardinal feature of alcohol-related brain dysfunction. *Neuroscience & Biobehavioral Reviews*, *54*, 38–45. doi:10.1016/J.NEUBIOREV.2014.07.023.

Platt, B., Kamboj, S. K., Italiano, T., Rendell, P. G., & Curran, H. V. (2016). Prospective memory impairments in heavy social drinkers are partially overcome by future event simulation. *Psychopharmacology*, *233*(3), 499–506. doi:10.1007/s00213-015-4145-1.

Rehm, J., Shield, K. D., Gmel, G., Rehm, M. X., & Frick, U. (2013). Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *European Neuropsychopharmacology*, *23*(2), 89–97. doi:10.1016/J.EURONEURO.2012.08.001.

Rensen, Y. C. M., Egger, J. I. M., Westhoff, J., Walvoort, S. J. W., & Kessels, R. P. C. (2017). The effect of errorless learning on quality of life in patients with Korsakoff's syndrome. *Neuropsychiatric Disease and Treatment*, *13*, 2867–2873. doi:10.2147/NDT.S140950.

Rensen, Y. C. M., Egger, J. I. M., Westhoff, J., Walvoort, S. J. W., & Kessels, R. P. C. C. (2019). The effect of errorless learning on psychotic and affective symptoms, as well as aggression and apathy in patients with Korsakoff's syndrome in long-term care facilities. *International Psychogeriatrics*, *31*(1), 39–47. doi:10.1017/S1041610218000492.

Reuster, T., Buechler, J., Winiecki, P., & Oehler, J. (2003). Influence of reboxetine on salivary MHPG concentration and cognitive symptoms among patients with alcohol-related Korsakoff's syndrome. *Neuropsychopharmacology*, *28*(5), 974–978. doi:10.1038/sj.npp.1300118.

Ridley, N. J., Draper, B., & Withall, A. (2013). Alcohol-related dementia: An update of the evidence. *Alzheimer's Research & Therapy*, *5*, 3. Retrieved from http://alzres.com/content/5/1/3.

Rochat, L., & Khazaal, Y. (2019). Cognitive remediation therapy of working memory in addictive disorders: An individualized, tailored, and recovery-oriented approach. *Expert Review of Neurotherapeutics*, *19*(4), 1–3. doi:10.1080/14737175.2019.1591950.

Ros-Cucurull, E., Palma-Álvarez, R. F., Cardona-Rubira, C., García-Raboso, E., Jacas, C., Grau-López, L., … Roncero, C. (2018). Alcohol use disorder and cognitive impairment in old age patients: A 6 months follow-up study in an outpatient unit in Barcelona. *Psychiatry Research*, *261*(October 2017), 361–366. doi:10.1016/j.psychres.2017.12.069.

Rupp, C. I. (2012). Cognitive remediation therapy during treatment for alcohol dependence. *Journal of Studies on Alcohol and Drugs*, *73*(4), 625–634. doi:10.15288/jsad.2012.73.625.

Rustembegović, A., Kundurović, Z., Sapcanin, A., & Sofic, E. (2003). A placebo-controlled study of memantine (Ebixa) in dementia of Wernicke-Korsakoff syndrome. *Medicinski Arhiv*, *57*(3), 149–150. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12858653.

Sachdeva, A., Chandra, M., Choudhary, M., Dayal, P., & Anand, K. S. (2016). Alcohol-related dementia and neurocognitive impairment: A review study. *International Journal of High Risk Behaviors and Addiction*, *5*(3), e27976. doi:10.5812/ijhrba.27976.

Sanvisens, A., Zuluaga, P., Fuster, D., Rivas, I., Tor, J., Marcos, M., … Muga, R. (2017). Long-term mortality of patients with an alcohol-related Wernicke-Korsakoff Syndrome. *Alcohol and Alcoholism* (*Oxford, Oxfordshire*), *52*(4), 466–471. doi:10.1093/alcalc/agx013.

Schwarzinger, M., Pollock, B. G., Hasan, O. S. M., Dufouil, C., Rehm, J., Baillot, S., … Group, Q. S. (2018). Contribution of alcohol use disorders to the burden of dementia in France 2008–13: A nationwide retrospective cohort study. *The Lancet Public Health*, *3*(3), e124–e132. doi:10.1016/S2468-2667(18)30022-7.

Snider, S. E., Deshpande, H. U., Lisinski, J. M., Koffarnus, M. N., LaConte, S. M., & Bickel, W. K. (2018). Working memory training improves alcohol users' episodic future thinking: A rate-dependent analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(2), 160–167. doi:10.1016/j.bpsc.2017.11.002.

Soler González, C., Balcells Oliveró, M., & Gual Solé, A. (2014). Alcohol related brain damage. State of the art and a call for action. *Adicciones*, *26*(3), 199–207. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25314035.

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addiction Biology*, *18*(2), 203–213. doi:10.1111/j.1369-1600.2011.00418.x.

Stevens, L., Goudriaan, A. E., Verdejo-Garcia, A., Dom, G., Roeyers, H., & Vanderplasschen, W. (2015). Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychological Medicine*, *45*(10), 2083–2093. 10.1017/S003329171500001X.

Sullivan, G. M., & Feinn, R. (2012). Using effect size—or why the *P* value Is not enough. *Journal of Graduate Medical Education*, *4*(3), 279–282. doi:10.4300/JGME-D-12-00156.1.

Svanberg, J., & Evans, J. J. (2013). Neuropsychological rehabilitation in alcohol-related brain damage: A systematic review. *Alcohol and Alcoholism*, *48*(6), 704–711. doi:10.1093/alcalc/agt131.

Swinnen, S. P., Puttemans, V., & Lamote, S. (2005). Procedural memory in Korsakoff's disease under different movement feedback conditions. *Behavioural Brain Research*, *159*(1), 127–133. doi:10.1016/j.bbr.2004.10.009.

Tuena, C., Serino, S., Dutriaux, L., Riva, G., Piolino, P., Tuena, C., … Piolino, P. (2019). Virtual enactment effect on memory in young and aged populations: A systematic review. *Journal of Clinical Medicine*, *8*(5), 620. doi:10.3390/jcm8050620.

Wanmaker, S., Leijdesdorff, S. M. J., Geraerts, E., van de Wetering, B. J. M., Renkema, P. J., & Franken, I. H. A. (2018). The efficacy of a working memory training in substance use patients: A randomized double-blind placebo-controlled clinical trial. *Journal of Clinical and Experimental Neuropsychology*, *40*(5), 473–486. doi:10.1080/13803395.2017.1372367.

Woods, A. J., Porges, E. C., Bryant, V. E., Seider, T., Gongvatana, A., Kahler, C. W., … Cohen, R. A. (2016). Current heavy alcohol consumption is associated with greater cognitive impairment in older adults. *Alcoholism: Clinical and Experimental Research*, *40*(11), 2435–2444. doi:10.1111/acer.13211.

World Health Organization (2018). Global status report on alcohol and health 2018.

Xu, W., Wang, H., Wan, Y., Tan, C., Li, J., Tan, L., & Yu, J.-T. (2017). Alcohol consumption and dementia risk: A dose–response meta-analysis of prospective studies. *European Journal of Epidemiology*, *32*(1), 31–42. doi:10.1007/s10654-017-0225-3.