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# Comparing neurocognitive function in individuals receiving chronic methadone or buprenorphine for the treatment of opioid dependence: A systematic review.

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*Summary*

**Introduction:** Agonist Opioid Treatments (AOT) have been, in comparison to healthy controls, associated with neurocognitive impairment in different domains. This review identifies differences in neurocognitive function as a result of treatment with either buprenorphine or methadone. **Method:** A qualitative and systematic literature review of published articles from 1946 to 29/2/2016 on neurocognitive function of patients prescribed buprenorphine or methadone and compared with healthy patients utilising the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. **Results:** The limited data demonstrate buprenorphine as presenting with fewer neurocognitive impairments, in cognitive impulsivity, cognitive flexibility and attention domains when compared with methadone. However both treatments modalities presented with more impairments in neurocognitive function domains, including short term memory, attention, cognitive flexibility, cognitive impulsivity, motor impulsivity and non planning impulsivity, when compared with healthy control groups. **Discussion:** The lack of published papers in comparing neurocognitive impairment between the treatment modalities limit interpretation of this systematic review. **Conclusion:** Further methodologically rigid and higher quality research into the neurocognitive effects of these treatment modalities in the opioid dependent populations, especially when in treatment, is urgently required.

*Key Words:* Neurocognitive Impairment; buprenorphine; methadone; treatment; opioid dependence

## 11. Introduction

Treatment for opioid (and opiate) addiction using agonist opioid treatments (AOT) (i.e. methadone and buprenorphine) have been associated with neurocognitive impairment in comparison to healthy controls.

For the purposes of this review we will use the term opioids to encompass both opiates and opioids. Opioids are widely used both legally in treatment, for their analgesic effects, and illicitly, for the psychotropic effects. The neurocognitive impairments associated with opioid use have already been documented [4]

Opioids are known to alter receptor sensitivity and expression, demonstrating a tolerance effect, but also display psychological dependence by altering the brains behavioural circuits. The receptors affected by opioids, are located through the brain and spinal cord, including the thalamus, hypothalamus, hippocampus, amygdala and the cerebral cortex [12],which are important for neurocognitive function, but are also connected to the reward and reinforcement area in the brain, the nucleus accumbens.

Opioid use has been demonstrated in the brain to increase oxidative stress, which contributes to neurotoxicity leading to neurocognitive impairment [7, 33].

In the review by Büttner and Mall, they noted reduced neuronal density in majority of patients dying from heroin overdoses due to respiratory depression and associated brain hypoxia [6].

Consideration of other contributing factors other

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than the direct opioid toxic effects on neurocognitive impairment needs to be considered. This can include bacterial and viral infection and other potential neuropathological insults [10]. These factors will not be reviewed in this systematic review.

To measure neurocognitive function in individuals the precise function being tested must be defined. Muriel Lezak, the author of the first book exploring neuropsychological assessment, wrote 'Direct observation of the fully integrated functioning of living human brains will probably always be impossible' [18]. Therefore, to assess neuropsychological function in the context of assessment, three domains (and subsequent sub-domains based on neurocognitive tests) need to be clearly defined to allow the objective observation of neurocognitive function in individuals:

- Intelligence
- Executive Function
- Memory and Learning

The use of an intelligence assessment allows an estimate the premorbid IQ of an individual. A vocabulary test is the primary assessment method use, e.g Shipley Institute of Living Scale (SILS) or Wechsler Adult Intelligence Scale – Revised & III [31, 38].

High level neurocognitive functions, known as Executive functions, allow for the control of behaviour to achieve a targeted outcome, this includes cognitive flexibility, cognitive planning, cognitive impulsivity, working memory and attention [5, 11, 36].

Memory and learning assesses an individual's ability to recall and make new memories. The Atkinson-Shiffrin model of memory proposes three distinct 'stores' of memory: sensory memory (lasting a few milliseconds: providing a buffer for sensory information and allows us to address information when required), short-term memory (lasting 12-30 seconds without rehearsal: primarily auditory in nature, can store around seven chunks of information for a few seconds without rehearsal [22] duration of storage can be increased with the use of a phonological loop), and long term memory which can be indefinite (ability to store information for a lifetime [2] and can be further split into declarative memory requiring conscious though and procedural memory requiring no thought).

A recent meta analysis looking at the effects of chronic methadone use identified global impairments in neurocognitive function relative to healthy participants [5].

This article aims to determine if there are differences in the effects on the neurocognitive function of patients being treated with either buprenorphine or methadone.

## 12. Methods

### *12.1. Literature Search*

A literature review identified articles relating to the neurocognitive effects of either buprenorphine

**Table 1:** Inclusion and exclusion criteria for studies used in the review

| Inclusion | Exclusion |
|---|---|
| Participants aged eighteen or over with chronic opioid dependence and currently engaged in an opioid maintenance programme | Cohorts with current uncontrolled poly-drug use (nicotine excluding). |
| Individuals needed to be compared to either healthy controls, abstinent individuals or another maintenance programme (methadone vs. buprenorphine) through the use of validated neuropsychological assessments. | Cohorts with a diagnosis of any Axis-1 psychiatric illness (excluding substance related disorders) as defined by DSM-IV/V (American Psychiatric Association 2000; American Psychiatric Association 2013). |
| Neuropsychological assessments needed to be identified and validated to allow for them to be classified into domains. If novel assessments were used a description of the cognitive functions assessed was used to classify by comparison to a defined assessment. | Cohorts with previous serious head injury. |
| Identified papers need to be of adequate quality matching the control/abstinent group to the maintained cohort, matching criteria should include: age, sex, years of education and years of heroin dependence | Articles with poor quality methodology, |
| Papers needed to report separate results for each cohort and test, papers which combined maintenance cohorts were excluded as it was not possible to extract the results required. | Cohorts including participants who were HIV serotype positive |

**Table 2:** Search Subject Headings

| | | | | |
|---|---|---|---|---|
| opioid related disorders OR | AND | neuropsychological tests/impairments/deficits OR | AND | methadone OR |
| substance related disorders OR | | | | buprenorphine OR |
| chronic drug dependence OR | | neurocognitive tests/deficits/impairments | | Subutex OR |
| substance withdrawal syndrome | | | | Suboxone |

or methadone on patients receiving Agonist Opioid Treatment (AOT) for opioid dependence. The cohorts chosen where either direct comparison between individuals treated with methadone or buprenorphine or those compared against a healthy control group. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were employed and the inclusion and exclusion criteria used have been tabulated in Table 1.

An electronic based search using a number of databases and incorporating articles published from 1946 to 29/2/2016 were used. The databases used where Ovid MEDLINE (1946 to 29/2/2016); EMBASE (1974 to 29/2/2016); PUBMED (1964 to 29/2/2016); PsychINFO (1980 to 29/2/ 2016). There were no language constraints employed.

The articles were identified using the search headings in Table 2.

The search terms 'neuropsychological tests' and 'neurocognitive tests' were then replaced with the sub-titles of neurocognitive domains e.g. Short Term Memory, Long Term Memory, Attention, Cognitive Flexibility, Cognitive Impulsivity, Motor Impulsivity and Non-Planning Impulsivity.

As this article is a literature review there was no requirement for ethical approval in relation to the study.

## 13. Results

### *13.1. Data analysis and study detail*

The literature search provided very few articles published on the comparison of effects of treatment on the neurocognitive function of patients being treated with buprenorphine or methadone.

With the very limited number of published articles offering direct comparisons (3 articles identified) between buprenorphine and methadone, a wider but indirect comparison of the effects on neurocognitive function were used from articles comparing either of the two therapeutic intervention against a healthy patient control group. The results of these studies were used to comment on the potential for neurocognitive impairment from the treatment with ORT against a control group.

### *13.2. Assessment of study quality*

The vast majority of selected articles for this review were assessed as fair in quality using the NIH Quality Framework for case-control studies (Table 3) (NIH 2014) with others ranging in quality from poor (2 articles) to good (1 article). All studies were observational case control studies.

### *13.3. Number of articles identified*

The initial literature search identified 426 articles from literature and other sources. Once duplicates were removed the total number of relevant manuscripts was reduced to 179. Titles and abstracts of 31 articles included in the accepted abstracts were screened for eligibility with an additional six articles included in the full text screening (Figure 1: QUORUM). The full text of the remaining 36 articles was assessed using the inclusion and exclusion criteria on Table 1. This assessment excluded a further 20 articles which failed to meet the inclusion criteria in the full text with the remaining 16 articles included in this review.

### *13.4. Cohorts identified*

The included articles described results from the direct comparison of 60 buprenorphine maintained individuals to 74 methadone maintained individuals from 3 published articles. When the search was extended to compare either methadone or buprenorphine maintained patients to a healthy control, there

**Table 3:** Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

| | | | Methadone Group | | | | | | | | Healthy Controls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Country | Quality | N | Mean Age (yrs) | Sex (nM/nF) | Education yrs | Mean IQ (sd) | Mean Opioid Use (yrs) | Methadone use (yrs) | Mean daily methadone dose (mg) | N | Mean Age (yrs) | Sex (nM/nF) | Education (yrs) | Mean IQ (sd) | Neuropsychological Tests Measured |
| Darke et al. (2000) | Australia | Fair | 30 | 35.8 | 18M / 12F | 11.2 | 91.5 (10.4) | 5 (minimum) | 5 (median) | 78.6 | 30 | 35.2 | 18M / 12F | 11.7 | 92.6 (-11.1) | WAIS-III; WMSR (PAL-I& II, VR-I & II subtests); CVLT; RCFT; COWAT; WCST |
| Mintzer et al (2002) | United States | Fair | 18 | 37.6 | 7M / 11F | 11.8 | 87.4 (2.7) | 15.3 | 3.78 | 67.2 | 21 | 34.9 | 10M / 11F | 12.1 | 94.0 (2.8) | DSST; TMT (A&B); 2BT; GT; ST; SILS (IQ) |
| Schindler et al. (2004) | Austria | Fair | 15 | 25.8 | 9M / 6F | Modal attainment Junior High School | n/a | 4.28 | 1.55 | 45.7 | Matched for age, sex and score in MAT (intelligence) | | | | | ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3) |

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/ Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMSR; Weschler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCFT; Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SILS= Shipley Institute of Living Scale; GT= Gambling Tast; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBCM= Three Dimensional Block Construction Model; SpTW= Spot the Real World;; CBT= Corsi Block Test; CRT=Choice Reaction Time; FTT= Finger Tapping Test; TOVA= Test of Variables of Attention; SS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Task; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austine Maze; n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matricies Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic- specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stess Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek–McHugh–Schluger–Kellogg Scale.

**Table 3:** Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rotherham-Fuller et al. (2004) | United States | Fair | 18 | 42.3 | n/a | 12.2 | 83.8 (9.7) | 0.5 (minimum) | 0.5 (minimum) | 61.6 | 19 | 37 | n/a | 13.6 | 92.1 (-13.2) | SILS (IQ); GT; WCST |
| Prosser et al. (2006) | United States | Fair | 29 | 37.9 | 23M / 6F | 13 | 8.05 (2.19) | 15.1 | 6.44 | 73.8 | 29 | 34 | 21M / 8F | 15.5 | 12.2 (-3.42) | WAIS-R (IQ); COWAT; ST; BVRT |
| Pirastu et al. (2006) | Italy | Fair | 30 | 35 | 29M / 1F | 8.37 | 85 | 15.5 | 8.3 | 66 | 21 | 34 | 14M / 7F | 10.9 | 104 (3.39) | WAIS-III (IQ); BVRT; WCST; IGT. |
| Soyka et al. (2011) | Germany | Poor | 24 | 32 | 16M / 8F | Modal attainment was "O" levels (n=10) | n/a | 11 | n/a | 56 | 25 | 29.8 | 14M / 11F | Modal attainment was general school leaving certificate (n=9) | n/a | ART-90 (PVT; TT15; Q1;RST3; DR2) |
| Lin et al. (2012) | Taiwan | Fair | 27 | 36.8 | 26M / 1F | 10.3 | n/a | 13.9 | 1.73 | 36 | 23 | 34 | 22M / 1F | 15.4 | n/a | SOMT; WSLT; BVRT; RRLET; SAVF; WAIS-R(digit span, arithmetic, symbol); Reitan Proverbs Test; 3DBCM |
| Liao et al. (2014) | Taiwan | Fair | 65 | 40.2 | 65M / 0F | 8.6 | n/a | 14.3 | 0.5 | 45 | 64 | 36.8 | 64M / 0F | 9.3 | n/a | SS; PES |
| Baldacchino et al. (2014) | United Kingdom | Good | 29 | 27.3 | 29M / 0F | 10.6 | 109 (7.6) | 8.8 | 1.3 | 55.8 | 28 | 24.1 | 28M / 0F | 15.4 | 118 (5.1) | NART (IQ); CGT; AGN; SOC |

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/ Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMSR; Weschler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCFT; Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SILS= Shipley Institute of Living Scale; GT= Gambling Tast; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBCM= Three Dimensional Block Construction Model; SpTW= Spot the Real World;; CBT= Corsi Block Test; CRT=Choice Reaction Time; FTT= Finger Tapping Test; TOVA= Test of Variables of Attention; SS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Task; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austine Maze; n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matricies Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic- specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stess Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek–McHugh–Schluger–Kellogg Scale.

**Table 4:** Characteristics of articles identified comparing buprenorphine maintenance patients to healthy controls.

| | | | Buprenorphine Group | | | | | | | | Healthy Controls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Country | Quality | n | Mean Age (yrs) | Sex (nM/nF) | Education (yrs) | Mean IQ (sd) | Mean Opioid Use (yrs) | Buprenorphine use (yrs) | Mean daily buprenorphine dose (mg) | n | Mean Age (yrs) | Sex (nM/nF) | Education (yrs) | Mean IQ (sd) | Neuropsychological Tests Measured |
| Schindler et al. (2004) | Austria | Fair | 15 | 25 | 5M / 10F | Modal attainment Junior High School | n/a | 3.63 | 0.93 | 10 | Matched for age, sex and score in MAT (intelligence) | | | | | ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3) |
| Pirastu et al. (2006) | Italy | Fair | 18 | 33 | 17M / 1F | 8.72 | 89.3 (-3.45) | 13.3 | 5.4 | 9 | 21 | 34 | 14M / 7F | 10.9 | 104 (-3.39) | WAIS-III (IQ); BVRT; WCST; IGT; RBANS |
| Messinis et al. (2009) | Greece | Fair | 18 | 36.5 | 15M / 3F | 11 | n/a | 12.8 | 0.67 | 6.78 | 34 | 35.7 | 27M / 7F | 11.5 | n/a | BNT; VFT; RAVLT; CTT; Ruff |
| Soyka et al. (2011) | Germany | Poor | 22 | 34.2 | 11M / 11F | Modal attainment was general school leaving certificate (n=9) or "O" Level attainment (n=9) | n/a | 11.6 | 0.19 | 10.4 | 25 | 29.8 | 114M / 11F | Modal attainment was general school leaving certificate (n=9) | n/a | ART-90 (PVT; TT15; Q1;RST3; DR2) |
| Shmygalev et al. (2011) | Germany | Fair | 11 | 36.6 | 28M / 2F | n/a | n/a | n/a | 5.5 | 7.7 | 90 | 37.1 | 84M / 6F | n/a | n/a | COG; DT; TAVT; VIG |

Abbreviations: n= Number of Participants; yrs= Years; nM/nF= Number Male/ Number Female; IQ= Intelligence Quotient; sd= Standard Deviation; mg- Milligrams; WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Scoring Task; IGT= Iowa Gambling Task; ART-2020= Act React Test System (MAT= Matricies Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stess Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

**Table 5:** Characteristics of articles identified comparing buprenorphine maintenance patients to methadone maintenance patients.

| | | | Buprenorphine Group | | | | | | | | Methadone Group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Country | Quality | n | Mean Age (yrs) | Sex (nM/nF) | Education (yrs) | Mean IQ (sd) | Mean Opioid Use (yrs) | Buprenorphine use (yrs) | Mean daily buprenorphine dose (mg) | n | Mean Age (yrs) | Sex (nM/nF) | Education (yrs) | Mean IQ (sd) | Mean Opioid Use (yrs) | Methadone Use (yrs) | Mean daily methadone dose (mg) | Neuropsychological Tests Measured |
| Schindler et al. (2004) | Austria | Fair | 15 | 25 | 5M / 10F | Modal attainment Junior High School | n/a | 3.63 | 0.93 | 10 | 15 | 25.8 | 9M / 6F | Modal attainment Junior High School | n/a | 4.28 | 1.55 | 45.7 | ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3) |
| Pirastu et al. (2006) | Italy | Fair | 18 | 33 | 17M / 1F | 8.72 | 89.3 (-3.45) | 13.28 | 5.4 | 9 | 30 | 35 | 29M / 1F | 8.37 | 85 | 15.53 | 8.3 | 66 | WAIS-III (IQ); BVRT; WCST; IGT. |
| Baewert et al. (2007) | Austria | Fair | 20 | 27 | 12M / 8F | n/a | n/a | 5.8 | 1.43 | 13.4 | 20 | 27.9 | 7M / 13F | n/a | n/a | 6.09 | 1.94 | 52.7 | ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3) |
| Soyka et al. (2011) | Germany | Poor | 22 | 34.2 | 11M / 11F | Modal attainment was general school leaving certificate (n=9) or "O" Level attainment (n=9) | n/a | 11.6 | 0.19 | 10.4 | 24 | 32 | 16M / 8F | Modal attainment was "O" levels (n=10) | n/a | 11 | 0.4 | 56 | ART-90 (PVT; TT15; Q1;RST3; DR2) |

Abbreviations: n=Number of Participants; yrs= Years; nM/nF= Number Males/Number Females; IQ= Intelligence Quotient; sd= Standard Deviation; mg=Milligrams; ART-2020= Act React Test System (MAT= Matricies Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic- specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); WAIS-III= Weschler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Sorting Test; IGT= Iowa Gambling Test; ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stess Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); n/a= Not Available.

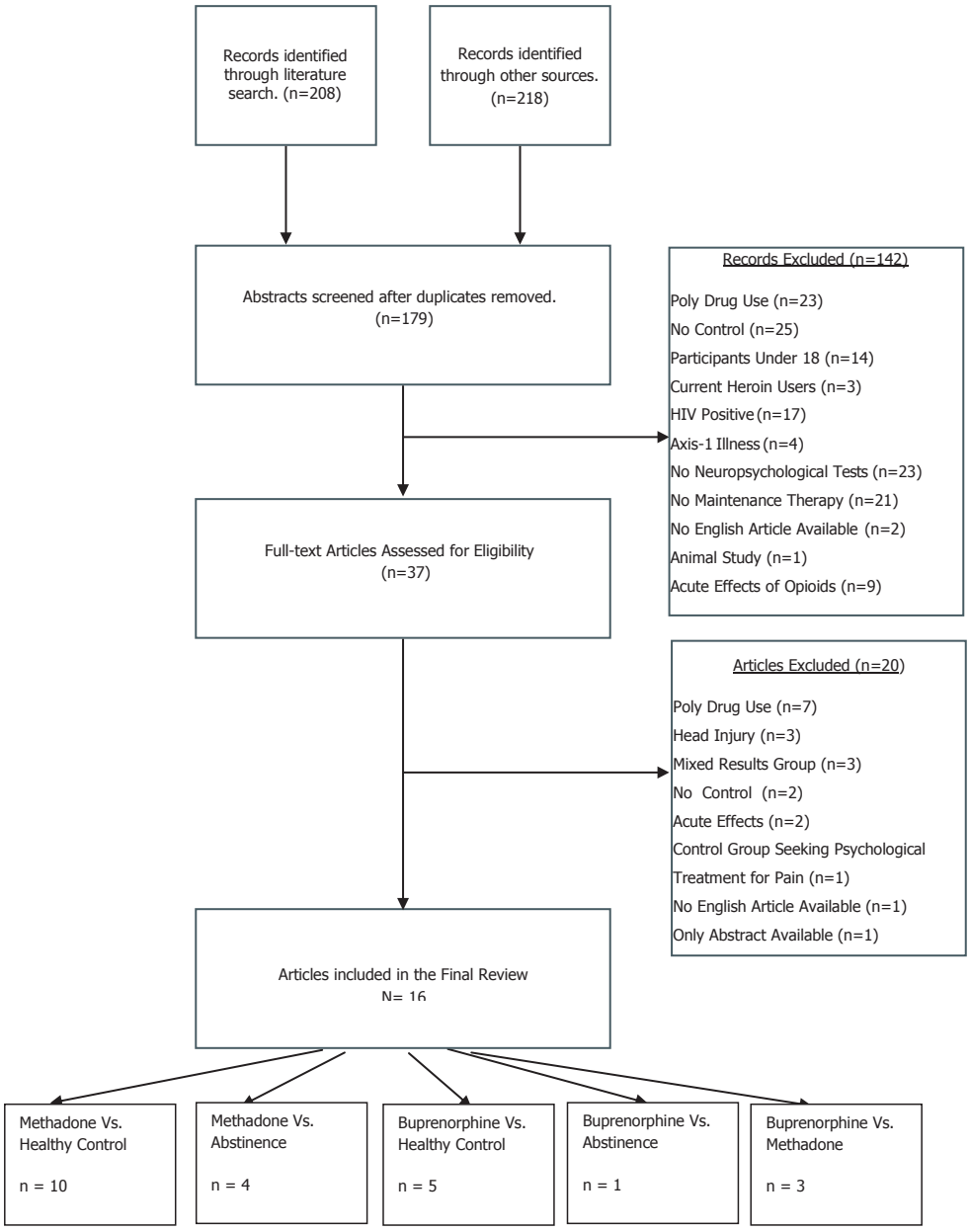


**Figure 1.** QUORUM

were the neurocognitive assessments of 279 methadone maintained individuals from 10 published articles and 84 individuals maintained on buprenorphine compared to healthy controls from 5 published papers [34], although one article is included in each comparison in the table as it compared healthy controls against methadone and buprenorphine and in addition a direct comparison between methadone and buprenorphine groups.

The papers included are shown in table 6.

*13.5. Neurocognitive impairments between groups*

In the articles directly comparing patients on ORT treatment [1, 25, 34], all except one domain (cognitive impulsivity) showed no significant differences between cognitive functioning in methadone and buprenorphine treated individuals.

*13.5.1. Cognitive impulsivity*

Buprenorphine maintained individuals scored significantly better ($p<0.05$) on measures of cognitive impulsivity than methadone maintained individuals in all three selected studies [1, 25, 34]. This is also supported by all other selected studies measuring this

**Table 6.** Articles included, comparison groups and neurocognitive domain

| Article | Outcome Group and Number (n) | Control Group Type and Number (n) | Intelligence | Short Term Memory | Long Term Memory | Attention | Cognitive Flexibility | Cognitive Impulsivity | Motor Impulsivity | Non Planning Impulsivity |
|---|---|---|---|---|---|---|---|---|---|---|
| Methadone Maintenance Papers | | | | | | | | | | |
| Darke et al. 2000 | 30 | 30 | ↓ - WAIS-III | ↓ - WMSR, CVLT, | ↓ - WSMR, CVLT | ↓ - WAIS-III | ↓ - COWAT, WCST | n/a | n/a | ↓ - RCFT (Copy) |
| Mintzer et al. 2002 | 18 | 21 | — - SILS | — - 2BT | n/a | ↓ - DSST | ↓ - TMT | ↓ - GT | n/a | n/a |
| Rotherham-Fuller et al. 2004 | 18 | 19 | — - SILS | n/a | n/a | n/a | — - WCST | ↓ - GT | n/a | n/a |
| Schindler et al. 2004 | 15 | Matched CON (See Demographic Table) | — - MAT | n/a | n/a | ↓ - DR2, Q1 — - FAT | □ - LL5, TT15 | ↓ - DR2 | n/a | n/a |
| Prosser et al. 2006 | 23 | 29 | ↓ - WAIS-III | ↓ - BVRT | n/a | — - ST | — - COWAT | n/a | n/a | n/a |
| Pirastu et al. 2006 | 30 | 21 | ↓ - WAIS-III | ↓ - BVRT | n/a | n/a | ↓ - WCST (errors) | ↓ - GT | n/a | n/a |
| Soyka et al. 2011 | 24 | 25 | n/a | ↓ - TT15 | n/a | — - PVT ↓ - Q1 (correct) | ↓ - TT15 | ↓ - DR2 | ↓ - RST-3 (Phase 1) ↓ - RST-3 (Phase 2) ↓ - RST-3 (Phase 3) | n/a |
| Lin et al. 2012 | 27 | 23 | — - WAIS-III | — - BVRT, SOMT, WSLT, RRLET, SAVF | — - RRLET, SAVF | — - WAIS-R | n/a | n/a | n/a | n/a |

Abbreviations: n= Number of Participants; MMT= Methadone Maintenance Programme; CON= Healthy Control; ABST= Protracted Abstinence; BUP= Buprenorphine Maintenance; WAIS-III= Weschler Adult Intelligence Scale; SILS= Shipley Institute of Living Scale; MAT = Matrices Test; NART= National Adult Reading Test; WSMR= Weschler Memory Scale - Revised; RCFT= Rey Complex Figure Test; 2BT= Two Back Test; BVRT= Benton Visual Retention Test;; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; CVLT= Californian Verbal Learning Test RAVLT= Rey Auditory Verbal Learning Test; RBANS= Repeatable Battery for the Assessment of Neurological Status; FAS= Fruits and Animals; DSST= Digit Symbol Substitution Test; ST= Stroop Test; CPT=Continuous Performance Test; WAIS-R Weschler Adult Intelligence Scale - Revised; SS= Stop Signal; PES= Post Error Slowing; FDT= Five Digit Test; Ruff= Ruff Selective Attention Test; CTT= Color Trails Test; COG= Attention Test; VIG= Vigilance Test; COWAT= Controlled Oral Word Association Test; WCST= Wisconsin Card Sorting Task; TMT= Trail Making Test; BNT= Boston Naming Test; VFT= Verbal Fluency Test; TAVT= Tachistoscopic Perception; GT= Gambling Test; CGT= Cambridge Gambling Test; FTT= Finger Tapping Test; AGN= Affective Go/No Go; DT=Determination Test; RCFT= Rey Complex Figure Test; AM=Austine Maze; SOC=Stockings of Cambridge; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

**Table 6.** Articles included, comparison groups and neurocognitive domain

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Liao et al. 2014 | 65 | 64 | n/a | n/a | n/a | — - SS , ↓ - PES | n/a | n/a | n/a | n/a |
| Baldacchino et al. 2014 | 29 | 28 | ↓ - NART | n/a | n/a | n/a | n/a | ↓ - CGT | — - AGN | ↓ - SOC |
| Buprenorphine Papers | | | | | | | | | | |
| Schindler et al. 2004 | 15 | Matched CON (See Demographic Table) | — - MAT | n/a | n/a | - DR2, FAT ↓ - Q1 (% incorrect) | ↓ - LL5, TT15 | — - DR2 | n/a | n/a |
| Pirastu et al. 2006 | 18 | 21 | ↓ - WAIS-III | ↓ - BVRT | n/a | n/a | — - WCST | — - GT | n/a | n/a |
| Messinis et al. 2009 | 18 | 34 | n/a | ↓ - RAVLT, RBANS | n/a | - Ruff ↓ - CTT2 | - BNT, VFT | n/a | n/a | n/a |
| Soyka et al. 2011 | 22 | 25 | n/a | ↓ - TT15 | n/a | — - PVT ↓ - Q1 (Correct) | ↓ - TT15 | — - DR2 | ↓ - RST-3 (Phase 1) ↓ - RST-3 (Phase 2) — - RST-3 (Phase 3) | n/a |
| Shmygalev et al. 2011 | 11 (Per-protocol) | 90 | n/a | n/a | n/a | — - COG | — - TAVT | n/a | ↓ - DT (Mean Reaction Time) | n/a |
| | Comparison Group (n) | Comparison Papers | | | | | | | | |
| Pirastu et al. 2006 | 18 | 30 | — - WAIS-III | — - BVRT | n/a | n/a | — - WCST | ↓ - GT | n/a | n/a |
| Baewert et al. 2007 | 20 | 20 | — - MAT | n/a | n/a | ↓ - DR2 — - Q1, FAT | ↓ - LL5, TT15 | ↓ - DR2 | — - RST3 | n/a |
| Key: | ↓ Significantly Lower Score ($p<0.05$), ↓ Significant Higher Score ($p<0.05$), ↓ No Significant Difference in score. (Outcome Group vs. Control or Comparison Group) | | | | | | | | | |

Abbreviations: n= Number of Participants; MMT= Methadone Maintenance Programme; CON= Healthy Control; ABST= Protracted Abstinence; BUP= Buprenorphine Maintenance; WAIS-III= Weschler Adult Intelligence Scale; SILS= Shipley Institute of Living Scale; MAT = Matrices Test; NART= National Adult Reading Test; WSMR= Weschler Memory Scale - Revised; RCFT= Rey Complex Figure Test; 2BT= Two Back Test; BVRT= Benton Visual Retention Test;; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; CVLT= Californian Verbal Learning Test RAVLT= Rey Auditory Verbal Learning Test; RBANS= Repeatable Battery for the Assessment of Neurological Status; FAS= Fruits and Animals; DSST= Digit Symbol Substitution Test; ST= Stroop Test; CPT=Continuous Performance Test; WAIS-R Weschler Adult Intelligence Scale - Revised; SS= Stop Signal; PES= Post Error Slowing; FDT= Five Digit Test; Ruff= Ruff Selective Attention Test; CTT= Color Trails Test; COG= Attention Test; VIG= Vigilance Test; COWAT= Controlled Oral Word Association Test; WCST= Wisconsin Card Sorting Task; TMT= Trail Making Test; BNT= Boston Naming Test; VFT= Verbal Fluency Test; TAVT= Tachistoscopic Perception; GT= Gambling Test; CGT= Cambridge Gambling Test; FTT= Finger Tapping Test; AGN= Affective Go/No Go; DT=Determination Test; RCFT= Rey Complex Figure Test; AM=Austine Maze; SOC=Stockings of Cambridge; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

cognitive domain and compared with healthy controls [3, 23, 25, 28, 30, 34]. There was however no significant difference found in cognitive impulsivity between buprenorphine maintained individuals and healthy controls [25, 30, 34].

*13.5.2. Cognitive flexibility*

In the three studies directly comparing methadone to buprenorphine treatment there were no significant differences in cognitive flexibility scores reported. However cognitive flexibility was more frequently reported as significantly impaired ($p<0.05$) in patients maintained on methadone, than those on buprenorphine when compared to healthy controls. Four of the ten selected studies [8, 23, 25, 34], showed impairment for methadone maintained individuals compared to healthy control. In comparison only one of five studies that reviewed cognitive flexibility in buprenorphine treated individuals identified impairment [34],with the other 4 papers finding no impairment in this domain in comparison to healthy controls.

*13.5.3. Motor impulsivity*

In the three papers conducting the direct comparison between methadone treatment and buprenorphine treatment, there were no reported differences in the motor impulsivity. However in the studies looking at comparison to healthy controls, both methadone and buprenorphine treated cohorts exhibited impairments in motor impulsivity when compared to healthy controls [32, 34].

*13.5.4. Attention*

One measure (DR2) in relation to the attention domain found buprenorphine individuals were less impaired than methadone in the papers comparing treatments against each other directly [1]. However the same paper found no significant difference on two other assessments of attention (Q1 & FAT). Soyka [34] also found no significant difference in attention test scores when comparing methadone to buprenorphine. Five articles that compared methadone to healthy controls identified a significant impairment in attention [8, 19, 23, 30, 34] with four buprenorphine comparison papers showed an impairment ($p<0.05$) in the attention domain [30, 21, 32, 34].

*13.5.5. Short term memory*

From the two direct comparison articles between methadone and buprenorphine cohorts that reported on Short Term Memory, there was no significant difference found [25, 34]. Short term memory was significantly impaired ($p<0.05$) relative to healthy controls in both methadone and buprenorphine cohorts. Four of the identified studies found a significant impairment ($p<0.05$) when methadone maintained individuals were compared to healthy controls [3, 8, 25, 27]. Three of the studies comparing buprenorphine to healthy controls showed significant impairment ($p<0.05$) in short term memory [21, 25, 34].

## 14. Discussion

*14.1. Summary of findings*

Buprenorphine maintained individuals demonstrate reduced impairment of cognitive impulsivity compared to those maintained on methadone. This was the most reliable conclusion drawn from the results as a significant difference was observed both in papers directly comparing methadone with buprenorphine and comparisons with control groups.

The attention domain shows that buprenorphine patients are less impaired than patients on methadone in the direct comparative studies. However, in the articles comparing methadone or buprenorphine to healthy controls, both treatments were shown to cause equal impairment. The differences between buprenorphine and methadone in relation to the attention domain could be due to the increased sedation experienced with a full opioid agonist in comparison to a partial agonist [29].

Cognitive flexibility was reported to be significantly less impaired ($p<0.05$) in buprenorphine maintained cohorts than methadone when compared to healthy controls. However this was not replicated in articles that directly compare the domain between methadone or buprenorphine maintained patients.

*14.2. Significance*

As the literature search demonstrated, using the strict criteria employed in this review, there is little evidence available currently to directly compare both buprenorphine and methadone maintenance therapies in relation to neurocognitive function. The articles that have been included highlights that there are differences between treatments and these may provide benefits for patients increasing the success of their treatment. However there is a lack of consistency in the tests employed in the research to date.

*14.3. Strength and Limitations*

The literature search found no Randomised Control Trials (RCTs) and all articles included are case-control studies. The lack of randomized blinded studies limits result reliability due to the possibility of increased bias [15]. Due to methodological difficulties, patients were not blinded to their interventional group with only two articles used a single blinded methodology [1, 30].

Articles were excluded if they included individuals affected by simultaneous illicit drug use or medication that might affecting neurocognitive function to minimise the effect of compounding factors. Most articles used different definitions of simultaneous drug use, showing a differing application of exclusion criteria between papers. Some conducted urinalysis over a period of months and others allowed for positive urine test if the individual was not experiencing acute effects. The most commonly identified additional substance was benzodiazepines, which are known to have effects on neurocognitive function [8, 28, 34, 37]. These mitigate the acute effects of benzodiazepines on the result of the neurocognitive tests and question the cause of any reported neurocognitive impairments in these studies. This becomes more important when comparing buprenorphine due to the limited number of papers available covering this area. The less robust exclusion criteria used in Soyka's [34] paper reduces the reliability of the results from this study. The results mirror those from the other three papers making this comparison [1, 25, 30], reducing the likelihood that benzodiazepine use caused these results. However it must be noted that benzodiazepine use is frequent amongst active heroin users, as well as those enrolled in maintenance opioid agonist replacement programmes. [16]. None of the studies considered the potential neurocognitive sequelae of chronic nicotine and/or cannabis use in this treatment seeking population.

The selected articles sample size lack consistency across the five studies investigating buprenorphine. They included 84 individuals, contrasting to 279 methadone maintained individuals across 10 selected studies. Potential root causes of this difference in articles identified are; (a) the limited period of time that buprenorphine preparations have been licensed for use in opioid dependence (mid-1990s for buprenorphine as opposed to methadone's availability since the 1960s) and (b) methadone being the preferential use of methadone as a first line treatment to opioid dependence [39].

The published articles are using small numbers studying individuals attending diverse treatment systems. A large degree of heterogeneity existed between studies, e.g. mean opioid use ranged from six months to over fifteen years between methadone cohorts [25, 28]. Other demographics followed similar trends, e.g. mean buprenorphine dose ranged from 6.78mg [21] to 13.4mg [1]. There were significant differences reported between comparable populations within individual selected studies. There were discrepancies in age, gender and educational attainment between populations [3, 20, 25, 27]. Significant differences in the completed educational years could have a profound effect on the neurocognitive test scores reported by these groups in the intelligence domain. Matching controls based on an estimate of their pre-morbid intelligence (IQ) will reduce this bias.

The time between administration of the maintenance dose and conducting the neurocognitive assessments needs to be considered as variations in the time delay may have different impairments on neurocognitive function due to the acute sedative effects of the treatment modality used [5]. One paper analysed the difference in scores between peak levels (1.5 hours after administration) and trough levels (20 hours after administration) for both methadone and buprenorphine. The combined results showed that individuals at trough levels performed significantly worse on the RST3 assessment of motor impulsivity [1]. In this review, the majority of studies included did not specify the time between administration of the last dose and neuropsychological test which impacts on repeatability and result interpretation. The large variation in duration of action means that individuals maintained on different opioids may experience the onset of withdrawal symptoms, at different times which may affect the neurocognitive assessment. Thus, if the assessment is conducted at the same time post administration; the methadone maintained cohort may collectively experience withdrawal symptoms earlier than the buprenorphine maintained cohort in direct comparison studies. Some studies screened for opioid withdrawal at the time of testing ensuring participants were not in withdrawal [30, 37], whilst others conducted assessments well within the duration of action of treatments [3, 17].

Multiple different cognitive domains are described and used in the literature. For the purposes of this enquiry the domains set out by Baldacchino et al. [4] were used.

Until a standardised system of domains and assessment exists there will always be discrepancies and variations in the tests used and subsequent result classification, damaging the integrity of conclusions

drawn from these studies

It is important to consider compounding factors affecting neurocognition, including head injury, alcohol use and overdose. Regression analysis was used by some papers to correct for variations of these factors. The rigorous inclusion criteria applied to papers is a strength of the review, and provides clear results comparing methadone/buprenorphine to a control or each other. This allowed a large array of data to be extracted from included papers. The majority of papers did not directly compare methadone to buprenorphine and further research into this area could address this factor.

Decreased neurocognitive test scores for both treatments were demonstrated in comparison to healthy controls. The comparison of each treatment option against healthy controls allows some inference to the effects of each treatment on the neurocognitive impairments experienced. The differences observed between the neurocognitive impairment and the prescribed treatment modality validates the need for further direct comparison research between the treatment options.

### *14.4. Clinical relevance*

The relevance of this review can be demonstrated in the application to driving ability. It is illegal to drive whilst impaired under the influence of any drug. England and Wales have a blood concentration limit for methadone of 500mcg/L of blood [9]. Buprenorphine has no defined concentration limit. Therefore if supported by further research and one treatment is proven to provide improved scores this could influence treatment choice. Therefore this review helps to identify better the current knowledge base when making clinical decisions on choice of opioid used for ORT to improve road safety and treatment retention.

The effect on neurocognitive function could be extrapolated to other functions and abilities and assist in making treatment choices for patients which are better suited and many patients report to a "clear head" with buprenorphine as opposed to "clouding" with methadone [14, 29, 35]. This subjectively based reduced neurocognitive impairment would be of greater benefit to the patients recovery and treatment on the grounds of the limited evidence identified. E. g. decreased neurocognitive impairment would be preferential for patients who are currently employed or actively seeking employment, those with a carers' role for either children or physically unwell individuals or those needing to be able to drive or operate heavy machinery. However for some patients a degree of cognitive impairment may be beneficial. E.g. states of increased boredom and "problematic thoughts that can increase the risk of relapse" [35]. This observation should be taken with extreme caution as this systematic review has highlighted the urgent need to conduct methodologically sound, unbiased and well powered studies to be able to identify better significant correlation between observed neurocognitive impairments and type of agonist opioid treatment used with clinical practice.

## 15. Conclusions

In conclusion, this systematic review of published literature into the neurocognitive function of individuals on methadone or buprenorphine maintenance treatment shows that there are fewer than expected reports of impaired neurocognitive function when patients are prescribed buprenorphine in comparison to methadone. There is a need for more rigorous and larger well matched longitudinal studies to reduce the variances caused due to opioid withdrawal influencing the result and to measure neurocognitive impairment of pharmacologically maintained individuals over time.

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