

APPENDIX 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year, Country	Main Findings and Authors' Conclusion																				
Randomized controlled trials																					
Neumann, 2013, US ¹⁵	<p>Main Findings: Comparison of SUB versus MET in patients with chronic pain + opioid addiction (13 patients in each group completed the study)</p> <table border="1" data-bbox="407 562 1377 716"> <thead> <tr> <th>Outcome</th> <th>SUB</th> <th>MET</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Positive urine test for opioids, n (%)</td> <td>5 (38.5)</td> <td>2 (15.4)</td> <td>NS</td> </tr> <tr> <td>Self-reported opioid use, n (%)</td> <td>5 (38.5)</td> <td>0</td> <td>0.039</td> </tr> <tr> <td>Treatment retention, n (%)</td> <td>13 (50.0)</td> <td>13 (46.4)</td> <td>NS</td> </tr> <tr> <td>Self-reported side effects, n (%)</td> <td>8 (61.5)</td> <td>9 (69.2)</td> <td>NS</td> </tr> </tbody> </table> <p>Authors' Conclusion: After 6 months treatment, no patients in the MET group compared to 5 in the SUB group reported illicit opioid use; other differences between the two groups were not significant.</p>	Outcome	SUB	MET	P value	Positive urine test for opioids, n (%)	5 (38.5)	2 (15.4)	NS	Self-reported opioid use, n (%)	5 (38.5)	0	0.039	Treatment retention, n (%)	13 (50.0)	13 (46.4)	NS	Self-reported side effects, n (%)	8 (61.5)	9 (69.2)	NS
Outcome	SUB	MET	P value																		
Positive urine test for opioids, n (%)	5 (38.5)	2 (15.4)	NS																		
Self-reported opioid use, n (%)	5 (38.5)	0	0.039																		
Treatment retention, n (%)	13 (50.0)	13 (46.4)	NS																		
Self-reported side effects, n (%)	8 (61.5)	9 (69.2)	NS																		
Otiashvili, 2013, Georgia ¹⁶	<p>Main Findings: Comparison of SUB versus MET in adult patients with opioid dependence (at 12 weeks)</p> <table border="1" data-bbox="407 930 1377 1140"> <thead> <tr> <th>Outcome</th> <th>SUB</th> <th>MET</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Positive urine test for opioid use, n (%)</td> <td>1 (0.2)</td> <td>6 (1.5)</td> <td>0.03</td> </tr> <tr> <td>Treatment retention, n (%)</td> <td>35 (87.5)</td> <td>33 (82.5)</td> <td>NR</td> </tr> <tr> <td>Adverse events, n</td> <td>108</td> <td>80</td> <td>0.003</td> </tr> </tbody> </table> <p>Authors' Conclusion: "Daily observed methadone or buprenorphine-naloxone are effective treatments for non-medical buprenorphine and other opioid use in Georgia." P. 1</p>	Outcome	SUB	MET	P value	Positive urine test for opioid use, n (%)	1 (0.2)	6 (1.5)	0.03	Treatment retention, n (%)	35 (87.5)	33 (82.5)	NR	Adverse events, n	108	80	0.003				
Outcome	SUB	MET	P value																		
Positive urine test for opioid use, n (%)	1 (0.2)	6 (1.5)	0.03																		
Treatment retention, n (%)	35 (87.5)	33 (82.5)	NR																		
Adverse events, n	108	80	0.003																		
Saxon, 2013, US ¹⁷ Hser, 2013, US ¹⁹ (secondary analysis of Saxon et al.)	<p>Main Findings: Comparison of SUB versus MET in adults with opioid dependence and normal liver function</p> <table border="1" data-bbox="407 1329 1279 1633"> <thead> <tr> <th>Outcome</th> <th>SUB</th> <th>MET</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Treatment retention, weeks (SD)</td> <td>18.5 (12.7)</td> <td>25.8 (10.0)</td> <td><0.0001</td> </tr> <tr> <td>Completion rate at 24 weeks, %</td> <td>46.1</td> <td>74.1</td> <td><0.01</td> </tr> <tr> <td>Serious adverse events, n (%)</td> <td>38 (5.2)</td> <td>45 (8.7)</td> <td>NS</td> </tr> </tbody> </table> <p>Authors' Conclusion: "MET participants were retained longer in treatment than BUP* participants." P. 71 * referred to SUB</p>	Outcome	SUB	MET	P value	Treatment retention, weeks (SD)	18.5 (12.7)	25.8 (10.0)	<0.0001	Completion rate at 24 weeks, %	46.1	74.1	<0.01	Serious adverse events, n (%)	38 (5.2)	45 (8.7)	NS				
Outcome	SUB	MET	P value																		
Treatment retention, weeks (SD)	18.5 (12.7)	25.8 (10.0)	<0.0001																		
Completion rate at 24 weeks, %	46.1	74.1	<0.01																		
Serious adverse events, n (%)	38 (5.2)	45 (8.7)	NS																		

First Author, Publication Year, Country	Main Findings and Authors' Conclusion																
Kamien, 2008, US ¹⁸	<p>Main Findings: Comparison of SUB versus MET in opioid-dependent patients</p> <table border="1"> <thead> <tr> <th data-bbox="407 457 781 485">Outcome</th> <th data-bbox="781 457 943 485">SUB</th> <th data-bbox="943 457 1105 485">MET</th> <th data-bbox="1105 457 1433 485">P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="407 485 781 726">Self-reported days of heroin use in the past days, change from baseline, mean (SE)</td> <td data-bbox="781 485 943 726">Low dose: from 26.9 (0.8) to 5.8 (2.4) High dose: from 26.3 (1.1) to 3.1 (1.7)</td> <td data-bbox="943 485 1105 726">Low dose: from 26.7 (0.8) to 9.0 (2.5) High dose: from 26.3 (0.9) to 4.3 (1.6)</td> <td data-bbox="1105 485 1433 726">=0.05 (low and high doses of study drugs were combined)</td> </tr> <tr> <td data-bbox="407 726 781 863">Treatment retention, weeks (SE)</td> <td data-bbox="781 726 943 863">Low dose: 12.1 (0.2) High dose: 12.5 (0.2)</td> <td data-bbox="943 726 1105 863">Low dose: 13.2 (0.2) High dose: 12.3 (0.2)</td> <td data-bbox="1105 726 1433 863">NR</td> </tr> <tr> <td data-bbox="407 863 781 911">Serious adverse events, n</td> <td data-bbox="781 863 943 911">1</td> <td data-bbox="943 863 1105 911">4</td> <td data-bbox="1105 863 1433 911">NR</td> </tr> </tbody> </table> <p>Authors' Conclusion: "Addiction and retention did not differ among groups. Buprenorphine-naloxone is a viable alternative to methadone in clinical practice." P. 5</p>	Outcome	SUB	MET	P value	Self-reported days of heroin use in the past days, change from baseline, mean (SE)	Low dose: from 26.9 (0.8) to 5.8 (2.4) High dose: from 26.3 (1.1) to 3.1 (1.7)	Low dose: from 26.7 (0.8) to 9.0 (2.5) High dose: from 26.3 (0.9) to 4.3 (1.6)	=0.05 (low and high doses of study drugs were combined)	Treatment retention, weeks (SE)	Low dose: 12.1 (0.2) High dose: 12.5 (0.2)	Low dose: 13.2 (0.2) High dose: 12.3 (0.2)	NR	Serious adverse events, n	1	4	NR
Outcome	SUB	MET	P value														
Self-reported days of heroin use in the past days, change from baseline, mean (SE)	Low dose: from 26.9 (0.8) to 5.8 (2.4) High dose: from 26.3 (1.1) to 3.1 (1.7)	Low dose: from 26.7 (0.8) to 9.0 (2.5) High dose: from 26.3 (0.9) to 4.3 (1.6)	=0.05 (low and high doses of study drugs were combined)														
Treatment retention, weeks (SE)	Low dose: 12.1 (0.2) High dose: 12.5 (0.2)	Low dose: 13.2 (0.2) High dose: 12.3 (0.2)	NR														
Serious adverse events, n	1	4	NR														
Non-randomized studies																	
McKeganey, 2013, UK ²⁰	<p>Main Findings:</p> <table border="1"> <thead> <tr> <th data-bbox="407 1098 813 1125">Outcome</th> <th data-bbox="813 1098 1008 1157">Percentage of patients SUB</th> <th data-bbox="1008 1098 1203 1157">Percentage of patients MET</th> <th data-bbox="1203 1098 1433 1125">P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="407 1157 813 1293">Days of heroin use in the past 90 days (change from 6-month timepoint to 14-month timepoint, mean (SD))</td> <td data-bbox="813 1157 1008 1293">38.64 (31.05) to 8.5 (12.52)</td> <td data-bbox="1008 1157 1203 1293">37.40 (38.66) to 24.15 (33.27)</td> <td data-bbox="1203 1157 1433 1293">NR</td> </tr> <tr> <td data-bbox="407 1293 813 1388">Treatment readiness at 6-month timepoint (score)</td> <td data-bbox="813 1293 1008 1388">2.96 (0.35)</td> <td data-bbox="1008 1293 1203 1388">3.13 (0.46)</td> <td data-bbox="1203 1293 1433 1388"><0.05</td> </tr> </tbody> </table> <p>Authors' Conclusion: "MET and SUB were highly and equally effective for preventing relapse to regular heroin use". P.97</p>	Outcome	Percentage of patients SUB	Percentage of patients MET	P value	Days of heroin use in the past 90 days (change from 6-month timepoint to 14-month timepoint, mean (SD))	38.64 (31.05) to 8.5 (12.52)	37.40 (38.66) to 24.15 (33.27)	NR	Treatment readiness at 6-month timepoint (score)	2.96 (0.35)	3.13 (0.46)	<0.05				
Outcome	Percentage of patients SUB	Percentage of patients MET	P value														
Days of heroin use in the past 90 days (change from 6-month timepoint to 14-month timepoint, mean (SD))	38.64 (31.05) to 8.5 (12.52)	37.40 (38.66) to 24.15 (33.27)	NR														
Treatment readiness at 6-month timepoint (score)	2.96 (0.35)	3.13 (0.46)	<0.05														
Rapeli, 2007, Finland ²¹	<p>Main Findings: Comparison of SUB versus MET in adult patients</p> <table border="1"> <thead> <tr> <th data-bbox="407 1591 651 1619">Outcome</th> <th data-bbox="651 1591 878 1619">SUB</th> <th data-bbox="878 1591 1105 1619">MET</th> <th data-bbox="1105 1591 1433 1619">P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="407 1619 651 1755">Attention (TAP Tonic Alertness, simple reaction time), mean (SD)</td> <td data-bbox="651 1619 878 1755">228 (13)</td> <td data-bbox="878 1619 1105 1755">258 (32)</td> <td data-bbox="1105 1619 1433 1755">NR, favored SUB</td> </tr> <tr> <td data-bbox="407 1755 651 1871">Working memory (WMS-III LNS), mean (SD)</td> <td data-bbox="651 1755 878 1871">8.7 (1.7)</td> <td data-bbox="878 1755 1105 1871">8.8 (2.6)</td> <td data-bbox="1105 1755 1433 1871">NR</td> </tr> </tbody> </table>	Outcome	SUB	MET	P value	Attention (TAP Tonic Alertness, simple reaction time), mean (SD)	228 (13)	258 (32)	NR, favored SUB	Working memory (WMS-III LNS), mean (SD)	8.7 (1.7)	8.8 (2.6)	NR				
Outcome	SUB	MET	P value														
Attention (TAP Tonic Alertness, simple reaction time), mean (SD)	228 (13)	258 (32)	NR, favored SUB														
Working memory (WMS-III LNS), mean (SD)	8.7 (1.7)	8.8 (2.6)	NR														

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	<p>Verbal memory, 14.8 (0.4) 14.6 (1.0) NR mean (SD)</p> <p>Authors' Conclusion: "To preserve cognitive function, the use of SUB may be more preferable to MET use." P. 2</p>
Economic evaluations	
Geitona, 2012, Greece ²²	<p>Retrospective data used for CEA were retrieved from 2 health authority databases. Assessment criteria for outcome assessment: the completion of treatment and number of deaths.</p> <p>CEA (ICER, 2008 euros):</p> <ul style="list-style-type: none"> - Effectiveness: % of treatment completion in SUB was 1.5-fold > than that in MET, % of deaths in SUB was 2.5-fold < than that in MET; - Cost for 1 year: €2,876 for SUB, €5,626 for MET. - ICER: €795.03 for SUB vs. MET for "treatment completion"; €1410.7 for "% of avoided deaths" <p>Sensitivity analyses: The variation of different individual cost parameters did not reverse the findings of the CEA.</p> <p>Author's conclusion: "Analysis of cost effectiveness demonstrated that buprenorphine-naloxone was the dominant therapy in terms of mortality avoidance and completion of treatment." (p. 77)</p>
Doran, 2005, Australia ²³	<p>Data were retrieved from an RCT. Assessment criteria for outcome assessment: changes in the number of heroin-free days between baseline and study end.</p> <p>CEA (ICER, 1998-1999 AUD):</p> <ul style="list-style-type: none"> - Effectiveness: change in number of heroin-free days between baseline and study end was 7.34 days in SUB, and 6.84 days in MET; - Cost for 6 months: AUD1,593 for SUB, AUD1,415 for MET. - ICER: AUD357 (confidence interval: -1,520 to 2,367) for SUB vs. MET for number of heroin-free days between baseline and study end. <p>Sensitivity analyses: The variation of different individual cost parameters (dosing times, price of BUP and variation in the amount of staff time spent in contact with patients) did not reverse the findings of nonstatistical significance of ICER in the CEA.</p> <p>Author's conclusion: "Adopting a provider perspective suggests that the observed difference between the cost-effectiveness of MET and the other treatments was not statistically significant, indicating that high-dose BUP and the BUP/NAL combination can provide a viable alternative to MET in the treatment of heroin dependence." (p. 583)</p>
<p>AUD=Australian dollar; CEA=cost-effectiveness analysis; ICER=incremental cost-effectiveness ratio; MET=methadone; MPD=Memory for Persons Data; NR=not reported; NS = not significant; RCT= randomized controlled trial; SD=standard deviation; SE=standard error of the mean; SUB = Suboxone; TAP=Test for Attentional Performance; WMS-III LNS=Wechsler Memory Scale -3rd version</p>	