

## Supplementary information to “Complementary therapies for clinical depression: an overview of systematic reviews”

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Supplementary table 1: Characteristics and outcomes of the included meta-analyses.

Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety	
<b>Acupuncture</b>									
<b>Manual acupuncture</b>	Smith 2018 <sup>51</sup>	MDD, CSD	49 RCTs	SB: 9 PB: 9 DB: 5 AB: 24 RB: 2 OB: 15	AMSTAR: 10	HAMD BDI	1.5-12 weeks	<p>Severity:</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than TAU (4 RCTs; SMD=-0.56; 95%CI=[-0.98,-0.15]; I<sup>2</sup>=62%; p=.03; N=458; ⊕○○○ very low<sup>a,c,d,e</sup>)</li> <li>– No sign. effects versus invasive SHAM (7 RCTs; SMD=-0.43; 95%CI=[-0.95,0.08]; I<sup>2</sup>=80%; p&lt;.001; N=418; ⊕○○○ very low<sup>a,c,d,e</sup>)#</li> <li>– Similar effects as SSRI/TCA (19 RCTs; SMD=-0.24; 95%CI=[-0.51,0.02]; I<sup>2</sup>=87%; p&lt;.001; N=1967; ⊕○○○ very low<sup>a,c,e</sup>)<sup>§</sup></li> <li>– Sign. greater effects as adjunctive to SSRI versus SSRI (8 RCTs; SMD=-1.32; 95%CI=[-2.09,-0.55]; I<sup>2</sup>=93%; p&lt;.001; N=539; ⊕○○○ very low<sup>a,c,e</sup>)</li> </ul> <p>Remission:</p> <ul style="list-style-type: none"> <li>– No sign. effects versus TAU (2 RCTs; RR=1.67; 95%CI=[0.77,3.65]; I<sup>2</sup>=0%; p=.44; N=94; ⊕○○○ very low<sup>a,d,e</sup>)</li> <li>– No sign. effects versus invasive SHAM (5 RCTs; RR=1.89; 95%CI=[0.75,4.75]; I<sup>2</sup>=63; p=.03; N=368; ⊕○○○ very low<sup>a,c,d,e</sup>)</li> <li>– Sign. smaller effects than SSRI/TCA (18 RCTs; RR=1.21; 95%CI=[1.06,1.39]; I<sup>2</sup>=18%; p=.24; N=1952; ⊕⊕○○ low<sup>a,e</sup>)<sup>§</sup></li> <li>– No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.33; 95%CI=[0.65,2.73]; I<sup>2</sup>=76%; p=.002; N=299; ⊕○○○ very low<sup>a,c,e</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>– Similar AEs as TAU (1 RCT; RR=0.89; 95%CI=[0.35,2.24]; I<sup>2</sup>=n.c.; N=320)</li> <li>– Similar AEs as invasive SHAM (1 RCT; RR=2.5; 95%CI=[0.15,40.37]; I<sup>2</sup>=n.c.; N=17)</li> <li>– Similar AEs adjunctive to SSRI versus SSRI (2 RCTs; SMD=-0.37; 95%CI=[-1.2,0.47]; I<sup>2</sup>=84%; N=150)</li> <li>– Sign. less AEs than SSRI (3 RCTs; SMD=-1.75; 95%CI=[-3.17,-0.32]; I<sup>2</sup>=96%; p p&lt;.001; N=481)<sup>#</sup></li> </ul>

Supplementary table 1: continued

2

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Electroacupuncture</b>	Smith 2018 <sup>51</sup>	MDD, CSD	21 RCTs	SB: 6 PB: 3 DB: 5 AB: 16 RB: 1 OB: 12	AMSTAR: 10	HAMD BDI	2-6 weeks	<p>Severity:</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than TAU (1 RCT; SMD=-1.26; 95%CI=[-2.10,-0.43]; I<sup>2</sup>=n.c.; N=30; ⊕○○○ very low<sup>a,c,d,e</sup>)</li> <li>– No sign. effects versus invasive SHAM (5 RCTs; SMD=0.12; 95%CI=[-0.14,0.38]; I<sup>2</sup>=0%; p=.82; N=251; ⊕○○○ very low<sup>a,d,e</sup>)<sup>#</sup></li> <li>– Sign. greater effects than SSRI/TCA (10 RCTs; SMD=-0.28; 95%CI=[-0.47,-0.09]; I<sup>2</sup>=33%; p=.14; N=995; ⊕⊕○○ low<sup>a,e</sup>)<sup>§</sup></li> <li>– Sign. greater effects as adjunctive to SSRI versus SSRI (5 RCTs; SMD=-0.84; 95%CI=[-1.16,-0.51]; I<sup>2</sup>=33%; p=.20; N=274; ⊕⊕○○ low<sup>a,e</sup>)</li> </ul> <p>Remission:</p> <ul style="list-style-type: none"> <li>– No sign. effects versus invasive SHAM (2 RCTs; RR=1.23; 95%CI=[0.35,4.29]; I<sup>2</sup>=20; p=.26; N=87; ⊕○○○ very low<sup>a,d,e</sup>)</li> <li>– Similar effects as SSRI/TCA (8 RCTs; RR=1.01; 95%CI=[0.92,1.11]; I<sup>2</sup>=0%; p=.43; N=966; ⊕⊕○○ low<sup>a,e</sup>)<sup>§</sup></li> <li>– No sign. effects as adjunctive to SSRI versus SSRI (5 RCTs; RR=1.17; 95%CI=[0.75,1.80]; I<sup>2</sup>=49%; p=.10; N=273; ⊕○○○ very low<sup>a,d,e</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>– Similar AEs as invasive SHAM (4 RCTs; RR=1.79; 95%CI=[0.99,3.25]; I<sup>2</sup>=16%; p=.31; N=244)</li> <li>– Sign. less AEs as adjunctive to SSRI versus SSRI (1 RCT; SMD=-3.39; 95%CI=[-4.27,-2.50]; I<sup>2</sup>=n.c.; N=50)</li> </ul>
<b>Herbs</b>									
<b>St. John's wort</b>	Linde 2008 <sup>150</sup>	MDD	29 RCTs	SB: 18 PB: 29 DB: n.r. AB: 29 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD MADRS	4-12 weeks	<p>Response (50%):</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than PLACEBO (18 RCTs; RR=1.48; 95%CI=[1.23,1.77]; I<sup>2</sup>=75%; p&lt;.001; N=3064; ⊕⊕⊕○ moderate<sup>c</sup>)</li> <li>– Similar effects as SSRI/TCA/TECA (17 RCTs; RR=1.01; 95%CI=[0.93,1.09]; I<sup>2</sup>=17%; p=.25; N=2810; ⊕⊕⊕○ moderate<sup>a</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>– Similar AEs as PLACEBO (14 RCTs; OR=0.98; 95%CI=[0.78,1.23]; I<sup>2</sup>=n.r.; N=2496),</li> <li>– Sign. less than ADMs (14 RCTs; OR=0.56; 95%CI=[0.43,0.74]; I<sup>2</sup>=n.r.; N=2663)</li> </ul>

Supplementary table 1: continued

3

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>St. John's wort</b> (continued)	Apaydin 2016 <sup>142</sup>	MDD	35 RCTs	SB: 9 PB: 27 DB: 5 AB: 26 RB: 3 OB: 33	AMSTAR: 9	HAMD	4-32 weeks	<p>Severity:</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than PLACEBO (16 RCTs; SMD=-0.49; 95%CI=[-0.74,-0.23]; I<sup>2</sup>=89%; p=n.r.; N=2888; ⊕⊕⊕○ moderate<sup>c</sup>)</li> <li>– Similar effects as ADM (14 RCTs; SMD=-0.03; 95%CI=[-0.21,0.15]; I<sup>2</sup>=74%; p=n.r.; N=2248; ⊕⊕○○ low<sup>a,c</sup>)</li> </ul> <p>Response (50%):</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than PLACEBO (18 RCTs; RR=1.53; 95%CI=[1.19,1.97]; I<sup>2</sup>=79%; p=n.r.; N=2922; ⊕⊕⊕○ moderate<sup>c</sup>)</li> <li>– Similar effects as ADM (17 RCTs; RR=1.01; 95%CI=[0.90,1.14]; I<sup>2</sup>=52%; p=n.r.; N=2776; ⊕⊕⊕○ moderate<sup>a</sup>)</li> </ul> <p>Remission:</p> <ul style="list-style-type: none"> <li>– No sign. effects versus PLACEBO (9 RCTs; RR=1.69; 95%CI=[0.63,4.55]; I<sup>2</sup>=94%; p=n.r.; N=1419; ⊕○○○ very low<sup>a,c,d</sup>)</li> <li>– Similar effects as ADM (7 RCTs; RR=1.17; 95%CI=[0.84,1.62]; I<sup>2</sup>=29%; p=n.r.; N=787; ⊕⊕⊕○ moderate<sup>a</sup>)</li> </ul> <p>Relapse:</p> <ul style="list-style-type: none"> <li>– No sign. effects versus PLACEBO (1 RCT; RR=0.70; 95%CI=[0.49,1.02]; I<sup>2</sup>=n.c.; N=426; ⊕○○○ very low<sup>a,c,d</sup>)</li> <li>– Similar effects as ADM (1 RCT; RR=4.17; 95%CI=[0.47,33.33]; I<sup>2</sup>=n.c.; N=241; ⊕○○○ very low<sup>a,c,d</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>– Similar AEs as PLACEBO (13 RCTs; OR=0.83; 95%CI=[0.62,1.13]; I<sup>2</sup>=n.r.; N=2600),</li> <li>– Sign. less than ADMs (11 RCTs; OR=0.67; 95%CI=[0.56,0.81]; I<sup>2</sup>=n.r.; N=1946)</li> </ul>
<b>Saffron</b>	Hausenblas 2013 <sup>147</sup>	MDD	5 RCTs	SB: 5 PB: 5 DB: 5 AB: 5 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD	6-8 weeks	<p>Severity:</p> <ul style="list-style-type: none"> <li>– Sign. greater effects than PLACEBO (2 RCTs; SMD=-1.62; 95%CI=[-2.14,-1.10]; I<sup>2</sup>=0%; p=n.r.; N=71; ⊕○○○ very low<sup>c,d,e</sup>)</li> <li>– Similar effects as SSRI/TCA (3 RCTs; SMD=-0.15; 95%CI=[-0.52,0.22]; I<sup>2</sup>=0%; p=n.r.; N=106; ⊕○○○ very low<sup>c,d,e</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>– No serious AEs</li> </ul>

Supplementary table 1: continued

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Curcuma</b>	Ng 2017 <sup>155</sup>	MDD, CSD	6 RCTs	SB: 3 PB: 3 DB: 3 AB: 2 RB: 2 OB: 1	AMSTAR: 6	HAMD, BDI	4-8 weeks	Severity: – Sign. greater effects than PLACEBO (6 RCTs; SMD=-0.34; 95%CI=[-0.56,-0.13]; I <sup>2</sup> =0%; p=.82; N=377; ⊕○○○ very low <sup>a,d,e</sup> )	– No serious AEs
<b>Chinese herbs</b>	Yeung 2014 <sup>162</sup>	MND	21 RCTs	SB: 5 PB: 11 DB: 9 AB: 21 RB: 20 OB: 18	AMSTAR: 4	HAMD	6-8,5 weeks	Severity: – Sign. greater effects than PLACEBO (4 RCTs; SMD=-1.27; 95%CI=[-1.67,-0.87]; I <sup>2</sup> =44%; p=.14; N=251; ⊕○○○ very low <sup>b,e</sup> )# – Similar effects as SSRI/SNRI/TCA/TECA (9 RCTs; SMD=0.17; 95%CI=[-0.12,0.46]; I <sup>2</sup> =82%; p<.001; N=1962; ⊕○○○ very low <sup>b,c,e</sup> )# Response (30%): – Sign. greater effects than PLACEBO (3 RCTs; RR=2.99; 95%CI=[2.18,4.10]; I <sup>2</sup> =0%; p=.53; N=281; ⊕○○○ very low <sup>c,d,e</sup> ) – Similar effects as SSRI/SNRI/TCA/TECA (10 RCTs; RR=1.00; 95%CI=[0.94,1.07]; I <sup>2</sup> =42%; p=.08; N=1635; ⊕○○○ very low <sup>b,c,e</sup> )	– Similar AEs as PLACEBO (3 RCTs; RR=1.29; 95%CI=[0.86,1.95]; I <sup>2</sup> =61%; p= n.r.; N=n.r.) – Sign. less AEs than ADMs (29 RCTs; RR=0.23; 95%CI=[0.16,0.33]; I <sup>2</sup> =59%; p= n.r.; N=n.r.)
<b>Light therapy</b>									
<b>Bright white light</b>	Tuunainen 2004 <sup>161</sup>	MND	18	SB: 2 PB: 0 DB: 13 AB: 1 RB: n.r. OB: n.r.	AMSTAR: 9	HAMD, GDS	1 day - 8 weeks	Severity: – Sign. greater effects than adjunctive to ADM than SHAM + ADM (18 RCTs; SMD=-0.20; 95%CI=[-0.38,-0.01]; I <sup>2</sup> =60%; p<.001; N=505; ⊕○○○ very low <sup>a,c,d</sup> ) Response: – No effects than adjunctive to ADM than SHAM + ADM (3 RCTs; RR=0.94; 95%CI=[0.61,1.46]; I <sup>2</sup> =69%; p=.004; N=71; ⊕○○○ very low <sup>a,c,d</sup> )	– No serious AEs
	Martensson 2015 <sup>152</sup>	SAD	8 RCTs	N.r.	AMSTAR: 5	HAMD, SIGH-SAD	2-6 weeks	Severity: – Sign. greater effects than SHAM (8 RCTs; SMD=-0.54; 95%CI=[-0.95,-0.13]; I <sup>2</sup> =n.r.; N=179; ⊕○○○ very low <sup>b,c,d,e</sup> )	– N.r.

Supplementary table 1: continued

5

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Meditative movement therapies</b>									
<b>Dance therapy</b>	Meekums 2015 <sup>153</sup>	MND	2 RCTs	SB: 1 PB: 0 DB: 1 AB: 2 RB: 2 OB: 1	AMSTAR: 9	HAMD	4-12 weeks	Severity: – Sign. greater effects as adjunctive to ADM versus ADM (2 RCTs; SMD=-1.06; 95%CI=[-1.46,-0.65]; I <sup>2</sup> =0%; p=.70; N=107; ⊕⊕○○ low <sup>d,c</sup> )#	– No serious AEs
<b>Qi Gong and Tai Chi</b>	Liu 2015 <sup>151</sup>	MDD, CSD	5 RCTs	N.r.	AMSTAR: 4	HAMD, GDS, CESD	10-16 weeks	Severity: – Sign. greater effects than TAU for Qi Gong (2 RCTs; SMD=-1.27; 95%CI=[-2.09,-0.45]; I <sup>2</sup> =74%; p=.05; N=120; ⊕○○○ very low <sup>b,c,d,e</sup> )* but no sign. effects for Tai Chi (3 RCTs; SMD=-0.61; 95%CI=[-1.55,0.34]; I <sup>2</sup> =78%; p=.01; N=120; ⊕○○○ very low <sup>b,c,d,e</sup> )*	– N.r.
<b>Yoga</b>	Cramer 2013 <sup>145</sup>	MDD, CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 1 RB: 5 OB: 3	AMSTAR: 8	HAMD, ZGS, GDS, BDI	4-8 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-1.03; 95%CI=[-1.90,-0.16]; I <sup>2</sup> =82%; p<.001; N=141; ⊕○○○ very low <sup>a,c,d,e</sup> )* – Sign. greater effects than EXERCISE (2 RCTs; SMD=-0.59; 95%CI=[-1.90,-0.16]; I <sup>2</sup> =68%; p=.08; N=108; ⊕○○○ very low <sup>a,c,d,e</sup> )	– N.r.
<b>Mindfulness-based interventions</b>									
<b>MBCT</b>	Strauss 2014 <sup>159</sup>	MDD	4 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	8-12 weeks	Severity: – Sign. greater effects than TAU (3 RCTs; SMD=-0.97; 95%CI=[-1.81,-0.12]; I <sup>2</sup> =72%; p=.03; N=115; ⊕○○○ very low <sup>b,c,d</sup> ) <sup>§</sup> – Similar effects as CBT (1 RCT; SMD=-0.16; 95%CI=[-0.75,0.43]; I <sup>2</sup> =n.c.; N=45; ⊕○○○ very low <sup>b,c,d</sup> ) <sup>§</sup>	– N.r.

Supplementary table 1: continued

6

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>MBCT</b> (continued)	Kuyken 2016 <sup>149</sup>	MDD	4 RCTs	SB: 4 PB: 0 DB: 3 AB: 4 RB: 4 OB: 4	AMSTAR: 6	SCID, BDI	60 weeks	Relapse: – Sign. greater effects than ADM (4 RCTs; HR=0.77; 95%CI=[0.60,0.98]; I <sup>2</sup> =0%; p=.92; N=669; ⊕⊕⊕○ moderate <sup>d</sup> )	– No serious AEs
<b>MBSR</b>	Bo 2017 <sup>144</sup>	CSD	5 RCTs	SB: 0 PB: 0 DB: 1 AB: 5 RB: 5 OB: n.r.	AMSTAR: 6	HAMD, GDS	8-12 weeks	Severity: – Sign. greater effects than TAU/enhanced TAU (5 RCTs; SMD=-1.09; 95%CI=[-1.41,-0.76]; I <sup>2</sup> =56%; p=.06; N=396; ⊕⊕○ low <sup>a,c</sup> )	– N.r.
<b>Music therapy</b>									
<b>Music therapy</b>	Zhao 2016 <sup>163</sup>	MND	8 RCTs	SB: 0 PB: 0 DB: 0 AB: 8 RB: 7 OB: 8	AMSTAR: 7	HAMD, GDS, HADS	4-52 weeks	Severity: – Sign. greater effects than TAU (5 RCTs; SMD=-0.57; 95%CI=[-1.03,-0.11]; I <sup>2</sup> =76%; p<.001; N=244; ⊕○○○ very low <sup>a,c,d</sup> )* – Sign. greater effects as adjunctive to ADM versus ADM (3 RCTs; SMD=-0.88; 95%CI=[-1.07,-0.68]; I <sup>2</sup> =0%; p=.63; N=257; ⊕⊕○○ low <sup>a,e</sup> )*	– N.r.
	Aalbers 2017 <sup>139</sup>	MDD, CSD	8 RCTs	SB: 2 PB: 1 DB: 1 AB: 7 RB: 2 OB: 3	AMSTAR: 11	HAMD	12 weeks	Severity: – Sign. greater effects than TAU (4 RCTs; SMD=-0.98; 95%CI=[-1.69,-0.27]; I <sup>2</sup> =83%; p<.001; N=219; ⊕○○○ very low <sup>a,c,d</sup> ) – Similar effects as CBT (4 RCTs; SMD=-1.28; 95%CI=[-3.57,1.02]; I <sup>2</sup> =96%; p<.001; N=131; ⊕○○○ very low <sup>a,c,d</sup> )	– Similar AEs as TAU (1 RCT; OR=0.45; 95%CI=[0.02,11.46]; I <sup>2</sup> =n.c.; N=79)

Supplementary table 1: continued

7

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Religious/spiritual therapies</b>									
<b>Faith-adapted CBT</b>	Anderson 2015 <sup>141</sup>	MDD, CSD	9 RCTs	SB: 0 PB: 0 DB: 4 AB: 4 RB: 9 OB: 0	AMSTAR: 7	N.r.	N.r.	Severity: – Sign. greater effects than TAU (6 RCTs; SMD=-0.69; 95%CI=[-1.21,-0.17]; I <sup>2</sup> =82%; p=.004; N=304; ⊕○○○ very low <sup>a,c,d</sup> ) <sup>§</sup> – Sign. greater effects than CBT (6 RCTs; SMD=-0.54; 95%CI=[-0.82,-0.25]; I <sup>2</sup> =0%; p=.78; N=199; ⊕⊕○○ low <sup>a,e</sup> ) <sup>§</sup>	– N.r.
<b>Supplements</b>									
<b>Inositol</b>	Mukai 2014 <sup>155</sup>	MDD	2 RCTs	N.r.	AMSTAR: 4	HAMD	4 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=0.17; 95%CI=[-0.33,0.66]; I <sup>2</sup> =0%; p=.93; N=78; ⊕○○○ very low <sup>b,d,e</sup> )	– Similar AEs as adjunctive to ADM (1 RCT; RR=3.21; 95%CI=[0.14,72.55]; I <sup>2</sup> =n.c.; N=36)
<b>Omega-3 fatty acids</b>	Appleton 2015 <sup>143</sup>	MDD	26 RCTs	SB: 15 PB: 6 DB: 19 AB: 8 RB: 16 OB: 25	AMSTAR: 9	HAMD, MADRS, BDI, GDS, HSCL, IDS	4-16 weeks	Severity: – Sign. greater effects than PLACEBO (25 RCTs; SMD=-0.30; 95%CI=[-0.50,-0.10]; I <sup>2</sup> =59%; p<.001; N=1373; ⊕○○○ very low <sup>a,c,d,e</sup> ) – Similar effects as SSRI (1 RCT; SMD=-0.08; 95%CI=[-0.70,0.54]; I <sup>2</sup> =n.c.; N=40; ⊕○○○ very low <sup>a,c,d,e</sup> ) Response (50%): – No sign. effects versus PLACEBO (15 RCTs; OR=1.39; 95%CI=[0.95,2.04]; I <sup>2</sup> =6%; p=.38; N=611; ⊕○○○ very low <sup>a,d,e</sup> ) – Similar effects as SSRI (1 RCT; OR=1.23; 95%CI=[0.35,4.31]; I <sup>2</sup> =n.c.; N=40; ⊕○○○ very low <sup>a,c,d,e</sup> ) Remission: – No sign. effects versus PLACEBO (6 RCTs; OR=1.38; 95%CI=[0.87,2.20]; I <sup>2</sup> =7%; p=.37; N=426; ⊕○○○ very low <sup>a,d,e</sup> )	– Similar AEs as PLACEBO (19 RCT; OR=1.24; 95%CI=[0.95,1.62]; I <sup>2</sup> =0%; p=.66; N=1207)

Supplementary table 1: continued

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Probiotics</b>	Huang 2016 <sup>148</sup>	MDD	1 RCTs	SB: 1 PB: 1 DB: 1 AB: 1 RB: 1 OB: 1	AMSTAR: 7	BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (1 RCT; SMD=-0.73; 95%CI=[-1.37,-0.09]; I <sup>2</sup> =n.c.; N=40; ⊕○○○ very low <sup>c,d,e</sup> )	– N.r.
<b>S-adenosyl methionine</b>	Galizia 2016 <sup>146</sup>	MDD	8 RCTs	SB: 2 PB: 4 DB: 4 AB: 3 RB: 8 OB: 8	AMSTAR: 9	HAMD	6-12 weeks	Severity: – No sign. effects versus PLACEBO (2 RCTs; SMD=-0.54; 95%CI=[-1.54,0.46]; I <sup>2</sup> =72%; p=.06; N=142; ⊕○○○ very low <sup>c,d,e</sup> ) – Similar effects as SSRI/TCA (5 RCTs; SMD=-0.01; 95%CI=[-0.22,0.21]; I <sup>2</sup> =43%; p=.14; N=821; ⊕⊕○○ low <sup>a,e</sup> ) <sup>§</sup> – Sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT; SMD=-0.59; 95%CI=[-1.06,-0.12]; I <sup>2</sup> =n.c.; N=73; ⊕○○○ very low <sup>c,d,e</sup> ) <sup>#</sup>	– Similar AEs as PLACEBO (2 RCTs; RR=0.70; 95%CI=[0.16,3.01]; I <sup>2</sup> =n.r.; N=142) – Similar AEs as adjunctive to ADM (1 RCT, RR=0.58; 95%CI=[0.10,3.28]; I <sup>2</sup> =n.c.; N=73) – Similar AEs as ADM (2 RCTs, RR=0.75; 95%CI=[0.20,2.79]; I <sup>2</sup> =n.r.; N=52)
<b>Tryptophan</b>	Shaw 2002 <sup>158</sup>	CSD	2 RCTs	SB: 2 PB: 2 DB: n.r. AB: 1 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD	3-12 weeks	Response: – Sign. greater effects than PLACEBO (2 RCTs; OR=4.10; 95%CI=[1.28,13.15]; I <sup>2</sup> =0%; p=.32; N=46; ⊕○○○ very low <sup>a,d,e</sup> )	– Sign. greater AEs than PLACEBO (2 RCTs; OR=7.41; 95%CI=[1.01,54.19]; I <sup>2</sup> =0%; p=1.0; N=64)
<b>Vitamin B9 (Folate)</b>	Taylor 2003 <sup>160</sup>	MDD	2 RCTs	SB: 0 PB: 2 DB: n.r. AB: 2 RB: n.r. OB: n.r.	AMSTAR: 8	HAMD	10-24 weeks	Severity: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (2 RCTs; SMD=-0.40; 95%CI=[-0.76,-0.05]; I <sup>2</sup> =0%; p=.96; N=124; ⊕○○○ very low <sup>a,c,d,e</sup> ) <sup>#</sup>	– Similar AEs as PLACEBO (1 RCT; RR=0.76; 95%CI=[0.55,1.05]; I <sup>2</sup> =n.c.; N=127)



Supplementary table 1: continued

9

	Included meta-analysis	Diagnosis	Number of studies	Studies with low risk of bias	Quality of the meta-analyses	Instruments used	Follow-up time	Pooled treatment effects (respective latest follow-up) with quality of evidence ratings according to GRADE	Safety
<b>Vitamin B9 (Folate)</b> (continued)	Almeida 2015 <sup>140</sup>	MDD	5 RCTs	SB: 4 PB: 5 DB: 4 AB: 3 RB: 4 OB: 1	AMSTAR: 6	HAMD, MADRS	4-52 weeks	Severity: – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (5 RCTs; SMD=-0.12; 95%CI=[-0.45,0.22]; I <sup>2</sup> =66%; p=.02; N=505; ⊕○○○ very low <sup>c,d,e</sup> ) Response (50%): – No sign. effects as adjunctive to SSRI versus PLACEBO + SSRI (4 RCTs; OR=1.18; 95%CI=[0.49,2.83]; I <sup>2</sup> =73%; p=.001; N=478; ⊕○○○ very low <sup>c,d,e</sup> ) Relapse: – Sign. greater effects as adjunctive to SSRI versus PLACEBO + SSRI (1 RCT, OR=0.33; 95%CI=[0.12, 0.94]; I <sup>2</sup> =n.c.; N=153; ⊕○○○ very low <sup>c,d,e</sup> )	– N.r.
<b>Vitamin D</b>	Shaffer 2014 <sup>157</sup>	MDD, CSD	2 RCTs	SB: 0 PB: 0 DB: 1 AB: 0 RB: n.r. OB: n.r.	AMSTAR: 7	HAMD, BDI	8 weeks	Severity: – Sign. greater effects than PLACEBO (2 RCTs; SMD=-0.60; 95%CI=[-1.19,-0.01]; I <sup>2</sup> =n.r.; N=149; ⊕○○○ very low <sup>a,c,d,e</sup> )	– N.r.
<b>Zinc</b>	Schefft 2017 <sup>156</sup>	MDD	3 RCTs	N.r.	AMSTAR: 5	HAMD, BDI	6-12 weeks	Severity: – Sign. greater effects as adjunctive to SSRI/TCA versus SSRI/TCA (3 RCTs; SMD=-0.66; 95%CI=[-1.06,-0.26]; I <sup>2</sup> =0%; p=.45; N=104; ⊕○○○ very low <sup>b,d,e</sup> )	– N.r.
Abbreviations: AB: Attrition bias; ADM: Antidepressant medication; AE: Adverse events; AMSTAR: Assessment of the Methodological Quality of Systematic Reviews tool; BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CESD: Center for Epidemiologic Studies Depression Scale; CSD: Clinical symptoms of depression (questionnaire based diagnosis); DB: Detection bias; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAMD: Hamilton Rating Scale for Depression; HR: Hazard ratio; HSCL: Hopkins Symptom Checklist Depression Scale; I <sup>2</sup> : Heterogeneity; IDS: Inventory of Depressive Symptomology; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MBSR: Mindfulness-based Stress Reduction; MDD: Major depressive disorder; MND: Mixed non-seasonal depression; N: Number of patients; N.c.: Not calculable because of only one included RCT; N.r.: Not reported; OB: Other bias; OR: Odds ratio; PB: Performance bias; RCT: Randomized controlled trial; RB: Reporting bias; RR: Risk ratio; SAD: Seasonal Affective Disorder; SB: Selection bias; SCID: Structured Clinical Interview; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders; SMD: Standard mean difference; SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitor; TAU: Treatment as usual; TCA: Tricyclic antidepressants; TECA: Tetracyclic antidepressants; ZGS: Zung Depression Scale.									

Supplementary table 1: continued

10

## Notes:

\*Newly calculated effect measure of selected RCTs meeting eligibility criteria;

#Newly calculated effect measure from mean differences (MDs);

§Newly calculated effect measure from originally separate/combined analyses.

<sup>a</sup>Downgraded one level because of study limitations (overall unclear or high risk of bias);

<sup>b</sup>Downgraded two levels because of study limitations (overall unclear or high risk of bias) and limitations of the meta-analysis (AMSTAR  $\leq 5$ );

<sup>c</sup>Downgraded one level because of inconsistency (significant heterogeneity or no replication of the results);

<sup>d</sup>Downgraded one level because of imprecision (confidence interval includes negligible or no effects or fewer than 250 participants were included in total);

<sup>e</sup>Downgraded one level because of a probably high risk of publication bias.