Depression in adults: treatment and management

Appendix J11:

study characteristics for evidence from previous versions of the guideline (St John's wort, seasonal affective disorder and relapse prevention)

Contents

Treatment of a new depressive episode

St John's wort - studies in 2004 guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Behnke2002 Y M C A	Allocation: Random (no details) Duration: 6 weeks Analysis: completer	Inpatients and outpatients. Age: 18-73. N=70. Diagnosis: ICD-10 Depression (F32), HRSD≥16 and ≤24. Mean baseline HRSD: SJW - 20 +-3.2, Fluoxetine - 20.7 +-2.9.	St John's wort (300mg = 2 x 150mg Hypericum perforatum: 0.450-0.495mg total hypericin per tablet) Fluoxetine (40mg)	HRSD-17 mean change scores Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Patients reporting adverse effects		B
Bergmann93 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. Age: 25-83. N= 80. Diagnosis: ICD-10 mild- moderate depressive episode. Mean baseline HRSD: SJW - 15.82 +-0.70, amitriptyline - 15.26 +-0.74	St John's wort Amitriptyline	HRSD-17 mean endpoint scores Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects Non-responders (patients not achieving ≥50% decrease in HRSD)		B
Brenner00 Y O I A/L	Allocation: Random (no details) Duration: 7 weeks Analysis: ITT	Outpatients. Age: 18-65. N=30. Diagnosis: DSM-IV major depression recurrent (21 patients) or single episode (9 patients) and HRSD≥17, baseline HRSD=21.5+-3.1	St John's wort (600mg -> 900mg LI 160) Sertraline (50mg -> 75mg)	HRSD-17 mean endpoint scores Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects	Dose of sertraline was below the therapeutic level.	B
Davidson02 YOI A/L P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT - LOCF	Outpatients. Age: 18+. N=340. Diagnosis: DSM-IV major depressive disorder and HRSD- 17≥20, baseline = 22.5-23.1	St John's wort (900 up to 1500mg LI 160: standardised to 0.12-0.28% hypericin) Sertraline (50mg up to 100mg) Placebo	HRSD-17 mean change scores Non-responders (patients not achieving ≥50 decrease in HRSD and 12≥HRSD≥9) Non-remitters (patients not achieving HRSD ≤ 8) Leaving the study early Leaving the study early due to side effects	Dose of sertraline was below the therapeutic level	B

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Hansgen1996 Y M C P	Allocation: Random (no details) Duration: 4 weeks Analysis: completer	Outpatients and primary care patients. N=108. Age: 18-70. Diagnosis: DSM-III-R major depression, HRSD≥16.	1. St John's wort (900mg = 3x300mg LI 160) 2. Placebo	1. HRSD mean endpoint scores Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Patients reporting adverse effects		B
Harrer94 Y O C A/L	Allocation: Random (no details) Duration: 4 weeks Analysis: Completers	Outpatients. N=102. Age: 24-65. Diagnosis: ICD-10 Moderate depressive episode, HRSD- 17≥16. Mean baseline HRSD: SJW - 20.5, maprotiline - 21.5	St John's wort (900mg = 3x 300mg LI 160) Maprotiline (75mg)	HRSD-17 mean endpoint scores Non-responders (patients not achieving ≥50% decrease in HRSD or HRSD≤10) Leaving the study early due to side effects Leaving the study early Patients reporting adverse effects	Dose of maprotiline was below the therapeutic level	B
Harrer99 E O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. N=161. Age: 60-80. Diagnosis: ICD-10 mild- moderate depressive episode, baseline HRSD 16.6-17.18	St John's wort (800mg = 4 x 200mg LoHyp-57: drug extract ratio 5-7:1) Fluoxetine (20mg)	HRSD-17 mean endpoint scores Non-responders (patients not achieving HRSD≤10 or >=50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects	ITT sample=149.	B
Kalb2001 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=72. Age: 18-65. Diagnosis: DSM-IV mild- moderate major depression and HRSD≥16. Mean baseline HRSD: SJW - 19.7 +-3.4, range 16-34; placebo - 20.1 +-2.6, range 16-26.	St John's wort (900mg = 3 x 300mg WS5572: drug extract ratio 2.5-5:1, 5% hyperforin) Placebo	HRSD-17 mean change scores Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects		B
Laakmann98 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: LOCF	Outpatients. N=147. Age: 18-65. Diagnosis: DSM-IV mild or moderate depression and HRSD-17≥17. Mean baseline HRSD: SJW - 20.9 +-3.1, placebo - 21.2 +-3.3	St John's wort (900mg = 3 x 300mg WS5572: 5% hyperforin) St John's wort (900mg = 3 x 300mg WS5573: 0.5% hyperforin) Placebo	HRSD-17 mean change score Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects	Data extracted for higher dose SJW (1) and placebo (3).	B

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Lecrubier02 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. Age: 18-66. N=375. Diagnosis: DSM-IV mild - moderate depression and 25=>HRSD≥18, baseline = 21.9 +-1.7, range: 18-27	1 St John's wort (900mg = 3 x 300mg WS5570: 0.12- 0.28% hypericin) 2. Placebo	HRSD-17 mean change scores Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Non-remitters (patients not achieving HRSD≤6) Patients reporting adverse effects		B
Philipp99 Y O I A P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT - LOCF	Primary care patients(?). N=263. Age: 18-65, mean=47. Diagnosis: ICD-10 moderate depressive episode and HRSD-17 ≥18, baseline=22.6 +-4.1	1. St John's wort (1050mg = 3 x 350mg STEI 300: 0.2- 0.3% hypericin, 2-3% hyperforin) 2. Imipramine (50mg -> 100mg) 3. Placebo	1. HRSD-17 mean change scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD) 3. Leaving the study early 4. Leaving the study early due to side effects		
Philipp99 Y O I A P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT - LOCF	Primary care patients(?). N=263. Age: 18-65, mean=47. Diagnosis: ICD-10 moderate depressive episode and HRSD-17 ≥18, baseline=22.6 +-4.1	1. St John's wort (1050mg = 3 x 350mg STEI 300: 0.2- 0.3% hypericin, 2-3% hyperforin) 5. Imipramine (50mg -> 100mg) 6. Placebo	5. HRSD-17 mean change scores 6. Non-responders (patients not achieving ≥50% decrease in HRSD) 7. Leaving the study early 8. Leaving the study early due to side effects		
Schrader00 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT - LOCF	Outpatients. N=240. Age: 18+, mean = 56.5. N=240. Diagnosis: mild - moderate depressive episode, 24≥HRSD≥16, mean HRSD = 19.5-19.65	St John's wort (500mg = 2 x 250mg ZE117 (drug extract ratio 4-7:1) Fluoxetine (20mg)	HRSD-21 mean change scores Non-responders (patients not achieving HRSD≤10 or ≥50% decrease in HRSD) Leaving the study early due to side effects Patients reporting adverse effects		B
Schrader98 Y ? I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	N=162. Age: 18+. Diagnosis: ICD-10 mild or moderate depressive episode and 16=< HRSD≤24. Mean baseline HRSD: SJW - 20.13, placebo - 18.76	St John's wort (500mg = 2 x 200mg ZE117: 0.5mg hypericin) Placebo	HRSD-21 mean change scores Non-responders (patients not achieving ≥50% decrease in HRSD or HRSD≤10) Patients reporting adverse effects		B

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Shelton 2001 Y O I P	Allocation: Random (no details) Duration: 8 weeks Analysis: ITT	Outpatients. N=200. Age: 18+. Diagnosis: DSM-IV major depressive disorder and HRSD- 17 ≥20. Mean baseline HRSD: SJW - 22, placebo - 23	St John's wort (900mg up to 1200mg, mean = 1110mg) Placebo	HRSD-17 mean endpoint scores Non-responders (patients not achieving ≥50% decrease in HRSD) Non-remitters (patients not achieving HRSD≤7) Leaving the study early Leaving the study early due to side effects	3 patients with co-morbid GAD, 4 pat-ients with comorbid social phobia. 12 patients (4 in SJW group, 8 in placebo group) were recei- ving psychotherapy.	B
van Gurp02 Y O I AL	Allocation: Random (no details) Duration: 12 weeks Analysis: ITT - LOCF	Outpatients. N=87. Age: 18-65. Diagnosis: DSM-IV major depression and HRSD≥16. Mean baseline HRSD: SJW - 18.9 +-3.6, sertraline - 19.7 +-3.5.	St John's wort (900mg up to 1800mg = 3-6 x 300mg @ 0.3% hypericum) Sertraline (50mg up to 100mg)	HRSD-17 mean change scores Leaving the study early Leaving the study early due to side effects	Only 21% patients received a therapeutic dose of sertraline	B
Volz2000 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=140. Age: 18-65. Diagnosis: DSM-IV mild- moderate depressive episode, HRSD-21≥18. Mean baseline HRSD: SJW - 21, placebo - 20.7	St John's wort (500mg = 2 x 250mg D-0496) Placebo	HRSD mean endpoint scores Leaving the study early Patients reporting adverse effects		B
Wheatley97 Y O I AL	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=165. Age: 20-65. Diagnosis: DSM-IV major depressive episode and 24=>HRSD≥17. Mean baseline HRSD: SJW - 20.6 +-2.1, amitriptyline - 20.8 +-2.3	St John's wort (900mg = 3 x 300mg LI 160 = 720-960µg hypericin) Amitriptyline (75mg)	Non-responders (patients not achieving HRSD<10 and ≥50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects	Dose of amitriptyline was below the therapeutic level	B
Witte1995 Y O I P	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=97. Age: 24-65. Diagnosis: ICD-10 moderate depressive episode.	St John's wort (200-240mg) Placebo	Non-responders (patients not achieving ≥50% decrease in HRSD) Leaving the study early		B
Woelk2000 Y O I A	Allocation: Random (no details) Duration: 6 weeks Analysis:	Outpatients. N=324. Age: 18+. Diagnosis: ICD-10 mild or moderate depressive episode and HRSD≥18, baseline = 22.1-22.4	St John's wort (500mg = 2 x 250mg ZE117: 0.2% Hypericin) Imipramine (150mg)	Non-responders (patients not achieving ≥ 50% decrease in HRSD) Leaving the study early Leaving the study early due to side effects Patients reporting adverse effects		B

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Characteristics of excluded studies

Study	Reason for exclusion
Agrawal1994	Unable to obtain full trial report
Halama1991	Includes patients with 'brief depressive reaction'; not clear how many
Harrer1991	Includes patients with 'brief depressive reaction'; not clear how many
Hoffmann1979	Inadequate diagnosis of depression
Hubner1994	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Johnson1991	Patients were not diagnosed with depression
Kniebel1988	Patients were diagnosed with dysthymia according to DSM-IV
Lehrl1993	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Lenoir1999	26% of patients not diagnosed with depression
Mueller1998	Not an RCT
Osterheider1992	Inadequate diagnosis of depression (abstract only no full publication)
Quandt1993	Unable to obtain full trial report
Reh1992	38/50 patients were diagnosed with brief depressive reaction
Rychlik2001	Not an RCT
Schlich1987	Inadequate diagnosis of depression
Schmidt1989	35% of patients not diagnosed with unipolar depression
Schmidt1993	Includes patients with 'brief depressive reaction'; not clear how many
Sommer1994	Inclusion criteria was ICD-09 diagnosis of neurotic depression or brief depressive reaction; the number of patients with each diagnosis was not given
Volz2002	Patients were not diagnosed with depression
Vorbach 1994	42% patients diagnosed with dysthymia or adjustment disorder
Vorbach97	'Lithium was allowed if it had been prescribed at least 3 months before the trial and was continued with an unchanged daily dose'; number of patients in each treatment group receiving lithium not specified

Seasonal affective disorder

Light therapy - new studies in the guideline update

Comparisons Included in this Clinical Question

Bright light + hypericum vs dim light + hypericum MARTINEZ1994	**Bright light + placebo pill vs dim light + fluoxetine** LAM2006F	**Bright light box vs placebo light box vs HMU light vs HMU placebo** LEVITT1996	**Bright light vs dawn simulation vs placebo dawn simulation** AVERY2001 TERMAN2006
Bright light vs deactivated negative ion generator DESAN2007	**Bright light vs dim light** ROSENTHAL1993	**Bright light vs group CBT vs combo light + CBT vs waitlist control** ROHAN2007	**Bright light vs modified group CBT vs bright light + modified group CBT** ROHAN2004
Bright vs medium vs dim light JOFFE1993	**Bright white light vs dim infrared light vs waitlist control** MEESTERS1999	**Bright white light vs dim red light** WILEMAN2001	**Gradual dawn vs rapid dawn** AVERY1993
Light room vs waitlist control RASTAD2008	**Morning bright light vs evening bright light vs alternating bright light** LAFER1994	**Morning vs afternoon bright light** AVERY2001A	**Morning vs afternoon vs evening bright light** MEESTERS1995
Morning vs evening bright light MEESTERS1993A	**Morning vs evening light vs deactivated negative ion generator** EASTMAN1998	**Morning vs evening light vs lowdensity negative ion generator** TERMAN1998	**Narrow-band blue light vs bright red light** STRONG2008

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes

AVERY1993 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 7 Setting: recruited through advertisements; US Notes: RANDOMISATION: stratified according to sex & quarter of menstrual cycle. 1 baseline week prior to treatment	n= 27 Age: Mean 35 Sex: 8 males 19 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode by DSM-III-R Exclusions: psychotropic medication in 2 weeks prior to study Notes: All participants had hypersomnia as part of their winter depression Baseline: HRSD-21 SAD subscale Gradual 17.1 (4.6) 13.1 (3.1) Rapid 18.6 (7.0) 16.1 (6.2)	**Data Used** Leaving treatment early due to lack of efficacy SAD subscale mean endpoint HRSD 21 mean endpoint Side effects reported Leaving treatment early for any reason **Data Not Used** CGI - not relevant Expectations measure - not relevant	**Group 1 N= 14** Dawn simulation - Gradual dawn: over 2 hours between 4-6am, incandescent reflector flood light increased intensity peaking at 250 lux as measured at distance of 122 cm from pillow **Group 2 N= 13** Dawn simulation - Rapid dawn: over 30 mins between 5.30-6am, incandescent reflector flood light increased intensity peaking at 0.2 lux as measured at distance of 122 cm from pillow	SIGN: 1+; funding NIMH
AVERY2001 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 42 & referral; US Notes: RANDOMISATION: stratified according to gender. 1 baseline week prior to treatment	n= 95 Age: Mean 41 Sex: 12 males 83 females Diagnosis: 100% major depression or bipolar with seasonal pattern by DSM-IV Exclusions: major medical or other psychiatric conditions, smokers, psychotropic medication in prev month, shift workers, routine wakening after 9am, those who drank > equiv of 4 cups of coffee/day, SIGH-SAD score <20 Notes: All participants had hypersomnia Baseline: not reported, >=20 on SIGH-SAD	**Data Used** Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 Leaving treatment early due to side effects Leaving treatment early for any reason Leaving treatment early due to lack of efficacy **Data Not Used** CGI - not relevant Expectations measure - not relevant	**Group 1 N= 33** Bright light - 10,000 lux light between 66.30am, eyes 30 cm from light box used while awake **Group 2 N= 31** Dawn simulation - white light with gradually increasing illuminance during sleep from 4.30-6am peaking at 250 lux, positioned 122 cm from pillow **Group 3 N= 31** Placebo dawn simulation - dim red light with gradually increasing illuminance during sleep from 4.30-6.30am peaking at 0.5 lux, positioned 122 cm from pillow	SIGN: 1+; funding NIMH

AVERY2001A Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 14 Setting: recruited through ads; US Notes: RANDOMISATION: no details. 1 baseline week prior to treatment	n= 31 Age: Mean 40 Sex: 3 males 28 females Diagnosis: 100% subsyndromal SAD Exclusions: signif medical problems, eye problems, major psychosocial stress, use of psychiatric medication in month prior to study, routine use of antihistamines, decongestants, asprin, appetite suppressants, sleeping medication Notes: No diagnoses of SAD but GSS score >=6 & SIGHSAD score >=12 Baseline: SIGH-SAD HDRS21 HDRS17 SAD Morning 23.8 (5.1) 11.8 (2.8) 10.3 (2.6) 12.0 (3.9) Afternoon 22.4 (7.4) 12.1 (5.1) 11.0 (5.0) 9.9 (3.2)	**Data Used** SAD subscale mean endpoint HAMD-17 mean endpoint SIGH-SAD mean endpoint Response: 50% reduction in SIGH-SAD Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** HRSD 21 mean endpoint - HRSD-17 used instead CGI - not relevant Sleep measures - not relevant VAS productivity - not relevant VAS mood - not relevant VAS energy - not relevant VAS alertness - not relevant	**Group 1 N= 16** Bright light (morning) - 2 hours of bright light 2,500 lux at 60 cm from light box, in morning (between 7am-12pm, average 9.26am) **Group 2 N= 15** Bright light (afternoon) - 2 hours of bright light 2,500 lux at 60 cm from light box, in morning (between 12-5pm, average 3.20pm)	SIGN: 1+; Royal Philips Electronics (part-funded)
DESAN2007 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 28 Setting: recruited through media ads & referral; 5 sites across US, Canada, Netherlands Notes: RANDOMISATION: balanced for site & gender. 1 baseline wEEk prior to treatment	n= 26 Age: Mean 46 Sex: 6 males 20 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-IV Exclusions: <18, >65, SIGH-SAD score<20, significant medical illness, retinal disease, pregnancy, use of photosensitising or mood altering medication, treatment for SAD in prior week, antidepressants within 4 weeks, psychotherapy within 3 months, organic mental disorder, panic, eating, OCD, PTSD, psychotic, bipolar, sun use disorder, previous unsuccessful trial with light, no informed consent, poor likelihood of complying with study, suicidal risk, habitual sleep pattern after 1am-9am Baseline: SIGH-SAD Light 28.0 (5.35) Control 25.1 (3.22)	**Data Used** Remission: SIGH-SAD <9 SIGH-SAD mean endpoint Leaving treatment early due to lack of efficacy Leaving treatment early for any reason **Data Not Used** Sleep measures - not relevant Expectations measure - not relevant	**Group 1 N= 15** Bright light - Litebook device - 60 LEDs, approx 1350 lux at 51 cm (spectral emission peak approximately 464 nm & 564 nm, emitted light appears white), used for 30 mins each morning as soon as poss upon arising and before 8am **Group 2 N= 11** Deactivated negative ion generator - Generated faint high-pitched whine at 51 cm, wrist strap worn which is connected to device, used for 30 mins each morning as soon as poss upon arising and before 8am	SIGN: 1+; funding The Litebook Company Ltd

EASTMAN1998				
Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 28 Setting: recruited through advertisements & local media; US Notes: RANDOMISATION: balanced for gender. 1 baseline week prior to treatment	n= 121 Age: Mean 37 Sex: 13 males 83 females Diagnosis: 100% SAD by Rosenthal criteria Exclusions: psychotropic medication, previous treatment with light or negative ions, complicating medical condition Notes: All patients required to have atypical symptoms of increased appetite/weight & increased sleep, & score >=21 on SIGH-SAD. Participants details only given for completers (96) Baseline: BDI-25 Morning 22.0 (9.2) Evening 23.6 (10.8) Placebo 25.7 (10.7)	**Data Used** BDI mean endpoint Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 Leaving treatment early for any reason **Data Not Used** Sleep measures - not relevant Expectations measure - not relevant	**Group 1 N= 41** Bright light (morning) - 6,000 lux light, participants sat 38 cm from light box containing 6 cool-white fluorescent lamps, used for 1.5 hours as soon as possible after waking. 6 days per week **Group 2 N= 40** Bright light (evening) - 6,000 lux light, participants sat 38 cm from light box containing 6 cool-white fluorescent lamps, used for 1.5 hours before bed (max 1 hour between end of treatment & bed). 6 days per week **Group 3 N= 40** Deactivated negative ion generator - generates white noise, has 3 small lights on the front which change rapidly between red & green, 2 generators set up on desk 38 cm from participant, used for 1.5 hours in morning. 6 days per week	SIGN: 1+; funding NIMH
JOFFE1993 Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 14 Followup: 1 week Setting: recruited by physician & self referral; 5 sites across Canada & US Notes: RANDOMISATION: stratified for medication status. There was a significant difference between results at different sites	n= 105 Age: Mean 40 Sex: 17 males 88 females Diagnosis: major depression or bipolar with seasonal pattern by DSM-III-R SAD by Rosenthal criteria Exclusions: light therapy in last 2 weeks, changes in dose of psychotropic medication, ophthalmological conditions, major medical illness, additional major psychiatric disorder, shift workers, unable to maintain stable sleep-wake pattern, HRSD-SAD 17 item score <=14 or 17 item score <=10 if total score <22 Baseline: HRDS-SAD Low 32.4 (6.3) Medium 32.2 (6.8) High 29.8 (5.8)	**Data Used** HRSD-SAD mean 1 week follow-up HRSD-SAD mean endpoint Response: 50% reduction in HRSD-SAD Remission: 50% reduction in HRSD-SAD & <=8 **Data Not Used** Expectations measure - not relevant	**Group 1 N= 33** Dim light - mean 67 lux (range 55-118 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily **Group 2 N= 38** Medium intensity light - mean 620 lux (range 520-762 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily **Group 3 N= 34** Bright light - mean 3,524 lux (range 2,8004,470 lux), delivered by light visor which consists of 2 incandescent light sources directed toward upper half of visual fields, used for 30 mins between 7-8.30am daily	SIGN: 1+; funding Bio-Brite

LAFER1994 Study Type: RCT Type of Analysis: Completer Blindness: Double blind Duration (days): Mean 7 Setting: Outpatients; US Notes: RANDOMISATION: randomised, no details Information on Screening Process: Referrals for treatment for SAD; no further details	n= 32 Age: Mean 35 Sex: 11 males 21 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: HAMD-31 < 20; history of psychosis, epilepsy, full manic episode, alcohol/drug misuse in past 3 months, suicidal, used antidepressants in past week	**Data Used** Response: 50% reduction in HAMD-31 Remission: HAMD-31 < 8 HAMD-31 mean endpoint	**Group 1 N= 9** Bright light (morning) - 2,500 lux for 2 hours **Group 2 N= 8** Bright light (evening) - 2,500 lux for 2 hours **Group 3 N= 15** Bright light - Alternating morning and evening; 2,500 lux for 2 hours [data not used]	SIGN: 1+; funding Massachusetts General Hospital and Harvard Medical School Psychiatric Neuroscience Fellowship
LAM2006F				194
Study Type: RCT Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 56 Setting: recruited by referral & advertisements in mood disorders clinics; 4 sites across Canada Notes: RANDOMISATION: codes centrally computer generated & stratified by site. 1 baseline week prior to treatment Info on Screening Process: 117	n= 96 Age: Mean 43 Sex: 32 males 64 females Diagnosis: 100% major depression or bipolar with seasonal pattern by DSM-IV Exclusions: <18 or >65 years, score <20 on HDRS17 or <14 if score on HRSD24 was >23, pregnant or lactating, women of childbearing age not using contraception, serious risk of suicide, organic mental disorder, substance misuse disorder, psychotic disorder, bipolar I, panic or GAD, serious unstable medical illness, retinal disease, severe allergies or multiple drug adverse reactions, current use of psychotropic drugs, beta blockers or antidepressants, previous treatment with fluoxetine or light therapy, psychotherapy in prior 3 months, shift workers, travel during study Baseline: HDRS Typical Atypical BDI-II Light 30.2 (5.5) 17.3 (3.7) 13.0 (3.6) 24.5 (8.5) Fuox 29.6 (5.3) 17.9 (3.4) 11.7 (4.3) 22.9 (9.3)	**Data Used** BDI II mean endpoint HRDS 7 (atypical symptoms) mean endpoint HAMD-17 mean endpoint HRDS 24 mean endpoint Response: 50% reduction in HRSD24 Remission: 50% reduction in HRSD & score <=8 Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason **Data Not Used** CGI - not relevant QoL Enjoyment and Satisfaction Questionnaire - not relevant QoL MOS SF-20 - not relevant	**Group 1 N= 48** Bright light - white fluorescent light box 10,000 lux at distance of 36 cm, used for 30 mins as soon as poss after waking between 7-8am daily Placebo - placebo pill identical to active treatment taken daily between 7-8am **Group 2 N= 48** Dim light - light box identical to active treatment but fitted with neutral density gel filter to reduce light to100 lux at distance of 36 cm, used for 30 mins as soon as poss after waking between 78am daily Fluoxetine. Mean dose 20 mg/day - fixed dose taken daily between 7-8am	SIGN: 1++; funding Canadian Institutes of Health Research (CIHR) and CIHR/Wyeth Postdoctroal Fellowship Award to one of the authors

LEVITT1996 Study Type: RCT Type of Analysis: completers Blindness: Single blind Duration (days): Mean 14 Setting: self-referred or referred by physician to outpatient Seasonal Mood Disorders Clinic; Canada Notes: RANDOMISATION: controlled by research nurse who did not interview any of the participants	n= 44 Age: Mean 35 Sex: 12 males 31 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: active major medical illness, eye condition that might preclude use of light therapy, travel toward equator in previous 2 weeks or during trial, unable to maintain stable sleep-wake cycle, any other axis I disorder except anxiety but including mania or hypomania, HAM-D-17 typical items score<=12, atypical items score <=10, SIGH-SAD total score <=18. Baseline: SIGH-SAD Typical Atypical Active lightbox 24.6 (7.7) 14.4 (3.4) 10.1 (5.1) Placebo lightbox 24.8 (6.0) 13.8 (2.5) 10.9 (4.2) Active HMU 23.2 (4.2) 13.7 (3.6) 9.5 (2.7) Placebo HMU 25.0 (4.1) 14.4 (1.8) 10.6 (4.2)	**Data Used** Expectations measure HAM-D-17 atypical items mean endpoint HAM-D-17 typical items mean endpoint SIGH-SAD mean endpoint Response: 50% reduction in SIGH-SAD Side effects reported Leaving treatment early for any reason	**Group 1 N= 10** Bright light - Active light box contained 4 fluorescent lamps, used for 30 mins/day before 9am, mean illuminance = 7,600 lux, range = 7,240-8,320 lux, eyes 30 cm from light source **Group 2 N= 12** No light - Placebo light box, identical to active light box but produced no light but makes similar hum to active light box, used for 30 mins/day before 9am **Group 3 N= 12** HMU light - Active head-mounted unit consists of 2 LEDs mounted on baseball cap, used for 30 mins/day before 9am, mean illuminance = 646 lux, range = 502-764 lux, eyes 8 cm from light source **Group 4 N= 10** HMU no light - Placebo head-mounted unit identical to active HMU but no light produced, used for 30 mins/day before 9am	SIGN: 1+; funding Mood Disorders Program, Clarke Institute of Psychiatry
MARTINEZ1994 Study Type: RCT Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 28 Setting: referral by physicians, self-referral following media ads; Germany Notes: RANDOMISATION: procedure not reported. 1 week washout prior to treatment Info on Screening Process: No details Baseline	n= 20 Age: Mean 46 Range 29-63 Sex: 7 males 13 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-III-R 30% Bipolar disorder (depressed phase) by DSM-III-R Exclusions: <18, >65 years; HAMD-21 < 16 HAM-D (SD) Bright light 21.9 (6.5); dim ilght 20.6 (3.9) Dim light 20.6 (3.9)	**Data Used** HRSD 21 mean endpoint	**Group 1 N= 10** Bright light - 3000 lux light for 2 hours a day, 90 cm from light Hypericum. Mean dose 900 mg/day - 3 coated tablets of hypericum extract per day each containing 300 mg, hypericum is plant extract thought to be capable of hastening the onset of antidepressant response to light therapy **Group 2 N= 10** Hypericum. Mean dose 900mg/day - 3 coated tablets of hypericum extract per day each containing 300mg, hypericum is plant extract thought to be capable of hastening the onset of antidepressant response to light therapy Dim light - <300 lux light for 2 hrs a day, 90cm from light	SIGN: 1+; funding unclear

MEESTERS1993A Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 5 Followup: 15 days follow-up Setting: Netherlands Notes: RANDOMISATION: balanced for gender. 4 baseline days prior to treatment	n= 30 Age: Mean 44 Sex: 7 males 20 females Diagnosis: 100% SAD by Rosenthal criteria Exclusions: medication in month prior to study, score<13 on BDI Notes: Participant info only reported for 27 participants who completed treatment. Baseline: HRSD21 HRSD7 BDI Morning 18.1 (4.8) 11.0 (4.7) 19.5 (5.1) Evening 15.8 (2.9) 13.7 (5.7) 22.6 (3.5)	**Data Used** Response: 50% reduction BDI & < 13 for 10 days Remission: 50% reduction in HRSD & score <=8 HRSD7 10 days post-treatment HRSD21 10 days post-treatment BDI 17 days post-treatment BDI 10 days post-treatment BDI 3 days post-treatment **Data Not Used** Activation-Deactivation Adjective Check List - not relevant Sleep Quality Scale - not relevant Stanford Sleepiness Scale - not relevant VAS-DEP - not relevant Adjective Mood Scale - not relevant Notes: 3 participants dropped out of study, however, the conditions these participants were randomised to is not reported	**Group 1 N= 16** Bright light (morning) - light box consisted of 4 full-spectrum fluorescent light tubes, 2,500 lux at distance of 90 cm, used for 3 hours/day between 9am-12pm on 5 consecutive days **Group 2 N= 11** Bright light (evening) - light box consisted of 4 full-spectrum fluorescent light tubes, 2,500 lux at distance of 90 cm, used for 3hours/day between 6-9pm on 5 consecutive days	SIGN: 1+; funding unclear. No relevant data - study not used

MEESTERS1995 Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 4 Followup: 11 days Setting: outpatients; Netherlands Notes: RANDOMISATION: participants balanced for gender & randomly assigned. 4 baseline days prior to treatment	n= 82 Age: Mean 38 Sex: 16 males 52 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: use of drugs in 3 weeks prior to experiment, score <13 on BDI on day before treatment. Notes: Participant info only reported for 68 participants who completed therapy. Baseline: HRSD HRSDadd BDI BDIadd Morn/eve 19.0 (3.8) 9.1 (4.4) 21.8 (4.5) 5.3 (2.5) Eve/morn 16.2 (4.0) 10.6 (4.7) 18.5 (3.9) 4.9 (2.3) Morning 16.9 (3.8) 9.9 (5.5) 25.0 (8.0) 5.1 (1.6) Evening 17.5 (1.1) 10.6 (2.4) 25.9 (8.6) 6.6 (3.2) Afternoon 15.9 (3.4) 12.0 (4.1) 20.3 (5.9) 5.6 (2.7)	**Data Used** Response: 50% reduction in HRSD & >8 BDIadd (atypical symptoms) 11 days posttreatment BDI mean 11 days post-treatment HRSDadd (atypical symptoms) 11 days posttreatment HRSD-21 mean 11 days post-treatment BDIadd (atypical symptoms) 4 days posttreatment BDI mean 4 days post-treatment HRSDadd (atypical symptoms) 4 days posttreatment HRSD-21 mean 4 days post-treatment **Data Not Used** VAS-DEP - not relevant Adjective Mood Scale - not relevant Notes: 14 participants dropped out of study but the conditions these participants were randomised to is not reported	**Group 1 N= 13** Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for 1st 2 days Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for last 2 days (interval between morning & evening light treatment is 36 hours) **Group 2 N= 14** Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for 1st 2 days Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for last 2 days (interval between evening & morning light treatment is 36 hours) **Group 3 N= 14** Bright light (morning) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30am for 4 days **Group 4 N= 12** Bright light (evening) - 10,000 lux light treatment at clinic for 30 mins a day between 8-8.30pm for 4 days **Group 5 N= 15** Bright light (afternoon) - 10,000 lux light treatment at clinic for 30 mins a day between 1-1.30pm for 4 days	SIGN: 1+; funding unclear. No relevant data - study not used

MEESTERS1999 Study Type: RCT Study Description: relapse prevention Type of Analysis: completers Blindness: No mention Duration (days): Mean 182 Setting: outpatients; Netherlands Notes: RANDOMISATION: 1st winter equal number of participants were assigned to 3 conditions, 2nd winter 2x as many assigned to light conditions as to control Info on Screening Process: 50	n= 46 Age: Mean 40 Sex: 11 males 27 females Diagnosis: 100% SAD by Rosenthal criteria 100% major depressive episode with seasonal pattern by DSM-III-R Exclusions: participants who developed depression at the start of the study, those using drugs, Notes: This study looks at relapse prevention. All participants diagnosed with SAD but only participants who had not yet developed winter depression at start of study (in October) were included. Baseline: Not reported, participants not depressed at start of trial	**Data Used** Leaving treatment early due to lack of efficacy Relapse: severe dep SIGH-SAD-SR >=40 Relapse: SIGH-SAD-SR >=20 in 2consec weeks Relapse: severe dep BDI >=22 Relapse: BDI >=13 in 2 consecutive weeks Leaving treatment early for any reason Notes: Significant difference between time of day light visor used between 2 groups.	**Group 1 N= 18** Bright light - 2,500 lux white light visor consisting of 2 krypton incandescent bulbs (12 cm from light source) worn for 30 mins/day between 6-9am, participants asked to choose their own fixed treatment time in their daily routine, mean 7.55am **Group 2 N= 18** Dim light - 0.18 lux infrared light visor consisting of 2 krypton incandescent bulbs (12 cm from light source) with filter worn for 30 mins/day between 6-9am, participants asked to choose their own fixed treatment time in their daily routine, mean 7.10am **Group 3 N= 10** Waitlist control - no light visor	SIGN: 1+; funding Bio Bright supplied equipment
RASTAD2008 Study Type: RCT Type of Analysis: completers Blindness: No mention Duration (days): Mean 21 Setting: recruited from earlier prevalence study; 4 sites across Sweden Notes: RANDOMISATION: restricted randomisation with probability factor of 0.8 was used, with separate lists for men and women Info on Screening Process: 312	n= 51 Age: Mean 46 Sex: 10 males 40 females Diagnosis: 100% major depressive episode with seasonal pattern by DSM-IV Exclusions: severe psychiatric or somatic disease, antidepressive medication, antibiotics, St Johns Wort, pregnancy, eye condition that precludes exposure to strong light, shift work, previous treatment with light therapy, unable to schedule 2-4 hours each morning for 10 consecutive weekdays, insufficient knowledge of Swedish Baseline: SIGH-SAD/SR Typical Atypical Light 21.8 (10.1) 14.2 (6.9) 7.6 (4.1) Waitlist 25.4 (8.1) 16.2 (5.8) 9.3 (4.0)	**Data Used** Atypical HAMD (8) mean endpoint HRSD 21 mean endpoint SIGH-SAD/SR mean endpoint Remission: <=8 SIGH-SAD/SR Response: 50% reduction in SIGH-SAD/SR Leaving treatment early for any reason	**Group 1 N= 26** Bright light - Light room at clinic, fullspectrum fluorescent lights on ceiling & walls, for 1.5-2 hours/day Mon-Fri between 6am and 9am in 4 different clinics. Light intensity varied depending on the clinic: 1,100 lux, 1,900 lux, 2,200 lux, 4,300lux. **Group 2 N= 25** Waitlist control - no light treatment	SIGN: 1+; funding Dalama County Council, Center for Clinical Research Dalama and Uppsala University

ROHAN2004 Study Type: RCT Blindness: Single blind Duration (days): Mean 42 Setting: Oupatients; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: Recruited via media advertisement; 265 people screened	n= 26 Age: Mean 51 Sex: 2 males 24 females Diagnosis: major depressive episode with seasonal pattern by DSM-IV Exclusions: Current psychological or psychiatric treatment; other Axis I disorders; plans for major vacations or absences during the study period; bipolar-type SAD	**Data Used** Remission: 50% reduction SIGH-SAD + HRSD21 <= 7 Remission: BDI-II <=8 Notes: Alternative remission criterion: HRSD-21 <= 2 + SIGH-SAD <= 10	**Group 1 N= 9** Bright light - 10,000 lux, 45 mins x 2/day 6-9 am and 6-9 pm **Group 2 N= 11** Group CBT - CBT tailored for SAD; group format 1.5 hour sessions twice per week over 6 weeks (12 sessions) **Group 3 N= 8** Bright light - As above CBT - As above	SIGN: 1+; funding Uniformed Services University of Health Sciences

ROHAN2007

Study Type: RCT

Type of Analysis: ITT

Blindness: Single blind

Duration (days): Mean 42

Setting: recruited through print & radio advertisements; US

Notes: RANDOMISATION: stratified for gender & race; used randomisation list prepared before recruitment

Info on Screening Process: 490

n= 61

Age: Mean 45

Sex: 6 males 55 females

Diagnosis:
100% major depressive episode with seasonal pattern by DSM-IV

Exclusions: current psychiatric treatment, another current axis I disorder, planned absences, bipolar type SAD, <18 years, SIGH-SAD score <20, HRSD score <10, atypical subscale score <5, failure to complete pre-treatment assessment.

Baseline:

	SIGH-SAD	HAMD	Atypical	BDI-II
Light	28.4 (6.1)	16.5 (5.2)	11.9 (3.8)	24.8 (8.1)
CBT	29.7 (5.3)	19.3 (4.6)	10.4 (4.0)	26.9 (10.7)
Combo	28.3 (5.6)	17.4 (5.7)	10.9 (3.1)	24.7 (5.9)
Waitlist	27.9 (6.1)	16.3 (3.9)	11.7 (3.7)	25.6 (5.7)

Data Used
BDI-II summer follow-up mean
Atypical HAM-D summer follow-up mean
HAM-D summer follow-up mean
SIGH-SAD summer follow-up mean
BDI II mean endpoint
Atypical HAMD (8) mean endpoint
HRSD 21 mean endpoint
SIGH-SAD mean endpoint
Remission: 50% reduction SIGH-SAD & HAMD <=7
Remission: BDI-II <=8
Leaving treatment early due to side effects
Leaving treatment early for any reason

Group 1 N= 16

Bright light - 10,000 lux white fluorescent light at 46 cm, used for 45 mins twice a day between 6am-9am and 6pm-9pm for 1st week, after this flexible dosing regarding time & duration as directed by consultant, average of 53 mins/day.

Group 2 N= 15

Group CBT - 1.5 hour sessions twice a week over 6 weeks (total 12 sessions) Groups of 4-8 participants, CBT specifically tailored to SAD

Group 3 N= 15

Group CBT - 1.5hr sessions twice a week over 6 wks (total 12 sessions) Groups of 4-8 participants, CBT specifically tailored to SAD

Bright light - 10,000 lux white fluorescent light at 46 cm, used for 45 mins twice a day between 6am-9am and 6pm-9pm for 1st week, after this flexible dosing regarding time & duration as directed by consultant, average of 53 mins/day.

Group 4 N= 15

Waitlist control - no treatment

SIGN: 1++; funding NIMH and Uniformed Services University of the Health Sciences

ROSENTHAL1993

Study Type: RCT

Type of Analysis: ITT

Blindness: Single blind

Duration (days): Mean 7

Followup: 1 week follow up

Setting: recruited through community referral channels & local news media; 3 sites across US

Notes: RANDOMISATION: stratified across centres & balanced according to concomitant medications & prev light therapy. 1 baseline week prior to treatment.

n= 55

Age: Mean 42

Sex: 9 males 46 females

Diagnosis:
100% SAD by Rosenthal criteria

100% lifetime history of major depression by DSM-III-R

Exclusions: poor physical health, retinal disease or cataracts, untreated hypothyroidism or serious medical conditions, changing dose of medications, shift workers & those unable to maintain consistent sleep schedules, light therapy in 2 weeks prior to trial

Baseline:

	SIGH-SAD	HDRS
Bright	31.0 (6.6)	16.8 (4.3)
Dim	31.2 (7.6)	17.7 (4.7)

Data Used
Side effects reported
Response: 50% reduction in SIGH-SAD
Response: 50% reduction in HRSD & >8
HRSD mean 1 week follow-up
HRSD 21 mean endpoint
SIGH-SAD mean 1 week follow-up
SIGH-SAD mean endpoint

Data Not Used
Sleep measures - not relevant
Expectations measure - not relevant
Notes: No mention of whether any participants left the study early

Group 1 N= 30

Bright light - Bright light visor (2 krypton incandescent bulbs of approx 6,000 lux (range 4,000-7,800 lux)), approx 6 cm from eyes for 60 mins (N=10) or 30 mins (N=20) 6.30-8.30am. (Time reduced following initial good results in control condition).

Group 2 N= 25

Dim light - Dim light visor (2 krypton incandescent bulbs of approx 400 lux (range 300-415 lux)), approx 6cm from eyes for 60 mins (N=11) or 30mins (N=14) 6.30-8.30am. (Time reduced following initial good results in control condition.)

SIGN: 1+; funding Bio-Brite

STRONG2008

Study Type: RCT

n= 30

Age: Mean 44

Sex: 7 males 23 females

Diagnosis:

Data Used
Leaving treatment early for any reason
SAD subscale mean change
HAMD-17 mean change
SIGH-SAD (HAMD-29) mean change

Data Not Used

Group 1 N= 15

Narrow-band blue light - 470 nm blue lightemitting diode unit; 176 lux; 5.45 E14 panels; 45 mins a day between 6am and 8am

Group 2 N= 15

SIGN: 1+; trial funded by Apollo Light Systems, but analysis funded elsewhere (unclear where)

Study Description: Open-label phase followed double-blind trial - data extracted from double-photon density/cm-squared/s; 4.5 x 3 inch blind trial only Type of Analysis: ITT LOCF Blindness: Double blind Duration (days): Mean 21 Setting: Unclear Notes: RANDOMISATION: randomised, no details Info on Screening Process: 35 met admission criteria - number screened unclear	100% Recurrent MDD episodes with a seasonal pattern by DSM-IV Exclusions: SIGH-SAD < 20; recently used light therapy; failed previous light therapy treatment; abnormal thyroidstimulating hormone values; co-occurring psychiatric disorder or medical condition that could affect mental status; ocular or dermatological health problems that might be affected by light therapy Notes: 19 people with pure SAD & 11 major depresison with seasonal intensification (post-hoc diagnosis); control group significantly older than treatment group (51 years vs 40 years) Baseline: SIGH-SAD 34.1 (5.6)	Leaving treatment early due to side effects - Unclear to which group leaver allocated Notes: Outcomes extracted for whole sample; only mean % change given for subsample with pure SAD	Red light - 650 nm red light-emitting diode unit; 201 lux; 3.17 E14 photon density/cmsquared/s; 4.5 x 3 inch panels; 45 mins a day between 6am and 8am	
TERMAN1998 Study Type: RCT Study Description: Cross-over study but precross data available Type of Analysis: Completer Blindness: Single blind Duration (days): Mean 14 Setting: Volunteers; US Notes: RANDOMISATION: randomised, no details Info on Screening Process: volunteers recruited through media announcements (including posters, and physician referrals	n= 158 Age: Mean 39 Range 18-59 Sex: 25 males 99 females Diagnosis: 100% SAD by National Institute for Mental Health criteria 100% mood disorder with seasonal pattern by DSM-III-R 100% major depressive episode by DSM-III-R 23% Bipolar disorder (depressed phase) by DSM-III-R Exclusions: other axis I disorders, suicide attempt within past 3 years, habitual sleep onset later than 1am or awakening later than 9am. Notes: Participant details & data reported for 124 completers who showed relapse during final withdrawal phase	**Data Used** SIGH-SAD mean endpoint **Data Not Used** Remission: <=8 SIGH-SAD/SR - Original N randomised uncler Notes: Continuous data from groups 1 and 2 only	**Group 1 N= 19** Bright light - morning light crossed over to morning light; 10,000 lux, 32 cm from eyes **Group 2 N= 19** Bright light - evening light crossed over to evening light; 10,000 lux, 32 cm from eyes **Group 3 N= 27** Bright light - morning light crossed over to evening light; 10,000 lux, 32 cm from eyes **Group 4 N= 20** Bright light - evening light crossed over to morning light; 10,000 lux, 32 cm from eyes **Group 5 N= 20** High density negative ions - 1.0 x 10 to power of 4 ions per cubic centimeter; continued same treatment post crossover; data not used **Group 6 N= 19** Low density negative ions - 2.7 x 10 to power of 6 ions per cubic centimeter; continued same treatment post crossover; data used as control group	SIGN: 1+, funding NIMH

TERMAN2006 Study Type: RCT Blindness: Single blind Duration (days): Mean 21 Setting: outpatients; US Notes: RANDOMISATION: procedure not reported. 1 baseline wk prior to treatment.	n= 126 Age: Mean 40 Sex: 22 males 77 females Diagnosis: 100% major depression or bipolar with seasonal pattern by DSM-III-R 100% SAD by Rosenthal criteria Exclusions: score of < 20 on SIGH-SAD, HAM-D-21 score of <10- or 8-item atypical score <5, poor medical health, consumption of alcohol, psychtropic medication or recreational drugs, comorbid axis I disorder, suicide attempt within 3 years, pregnancy, habitual sleep onset later than 1am or wake-up time later than 9am, past treatment with light or negative ions. Notes: Participant details and data reported only for 99 participants who completed trial and either remained depressed or relapsed during withrawal phase	**Data Used** Response: 50% reduction in SIGH-SAD Remission: SIGH-SAD <=8 HRSD 21 mean endpoint SIGH-SAD mean endpoint Leaving treatment early for any reason	**Group 1 N= 23** Bright light - Light box 10,000 lux for 30 mins within 10 mins of rising, 31 cm from head of bed **Group 2 N= 25** Dawn simulation - From 0.0003 lux to 350 lux designed to simulate sunrise on 5 May at 45 degrees north latitude outdoors under tree cover over 3.5 hours **Group 3 N= 26** High density negative ions - Not extracted **Group 4 N= 27** Dawn pulse control - Control for dawn simulation: trapezoidal light pulse of 250 lux (13 mins) before wake-up time **Group 5 N= 25** Low density negative ions - Not extracted	SIGN: 1+; funding unclear (light boxes donated)

WILEMAN 2001 Study Type: RCT Type of Analysis: completers Blindness: Open Duration (days): Mean 28 Setting: recruited via GPs; Scotland Notes: RANDOMISATION: using minimisation to ensure balance between groups for age, gender & current antidepressant therapy	n= 59 Age: Mean 41 Sex: 5 males 52 females Diagnosis: major depressive episode with seasonal pattern by DSM-IV Exclusions: SIGH-SAD score < 15, <16, >64 Baseline: SIGH-SAD white 34.91 (9.9) red 34.69 (7.9)	**Data Used** Expectations measure Response: 50% reduction in SIGH-SAD/SR Response: total SIGH-SAD-SR score <18 & atyp <8 Response: 50% reduction in SIGH-SAD-SR & <=8 SIGH-SAD/SR mean endpoint	**Group 1 N= 33** Bright light - Bright white light of 10,000 lux at 51 cm for 30 mins/day for the 1st week, 45 mins/day for the 2nd week and 1 hour/day for last 2 weeks. Participants were advised that most beneficial time is morning but that any time before 7pm is acceptable. **Group 2 N= 26** Dim light - Dim red light of 500 lux at 51 cm for 30 mins/day for the 1st week, 45 mins/day for the 2nd week and 1 hour/day for last 2 weeks. Participants were advised that most beneficial time is morning but that any time before 7pm is acceptable.	SIGN 1+; funding Chief Scientist Office of the Scottish Executive Department of Health

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
BENEDETTI2003	Not SAD - patients did not fulfil criteria for seasonal pattern
BIELSKI1992	Does not report whether participants were randomised
BRAINARD1990	Cross-over trial, data not extractable
BROWN2001A	Not SAD - non-seasonal depression
DOGHRAMJI1990	Cross-over design; fewer than 10 participants in each condition (2-hour light therapy vs 4-hour light therapy)
EASTMAN1992	Does not report whether participants were randomised
GLOTH1999	No extractable data; fewer than 10 participants per arm (vitamin D vs phototherapy)
GROTA1989	No extractable data; fewer than 10 participants in each condition (bright light vs dim light)
HOEKSTRA2003	No control condition, all participants received light therapy, compares SAD patients with control group

JACOBSEN1987A	Cross-over study; fewer than 10 participants in each condition (early morning light vs early afternoon light)
JAMES1985	Cross-over study; fewer than 10 participants in each condition (bright light vs dim light)
KOORENGEVEL2001	Intervention not relevant to guideline (extraocular light)
LAM1991	Cross-over study; fewer than 10 participants in each condition (ultraviolet light vs ultra-violet-blocked light vs dim light)
LAM2004	Not an RCT (augmentation or switch: citalopram vs bupropion)
LEPPAMAKI2002A	Light and exercise combination therapy, in exercise review
LINGJAERDE1998	No relevant outcomes reported
LOVING2005	Not SAD - non-seasonal depression
LOVING2005A	Not SAD - non-seasonal depression
MAGNUSSON1991	Cross-over study; fewer than 10 participants in each condition (bright white light vs dim red light)
MARTINY2004B	No control condition, all participants received light therapy
MCGRATH1990	Cross-over trial - data not extractable
MICHALON1997	No relevant outcomes reported
NAGAYAMA1994	Non-randomised design; fewer than 10 participants in each condition (bright light vs dim light)
NORDEN1993	Cross-over trial - data not extractable
OREN1991	Cross-over study; fewer than 10 participants in each condition (green light vs red light)
RAO1990	Not SAD - non-seasonal depression
ROSENTHAL1984	Cross-over study; fewer than 10 participants in each condition (bright light vs dim light)
ROSENTHAL1985	Cross-over study; 20 out of 22 with bipolar disorder
ROSENTHAL1987	Cross-over study - data not extractable
ROSENTHAL1988	Not light therapy - atenolol vs placebo
RUHRMANN1998	17.5% participants (7 out of 40) have a diagnosis of bipolar disorder
SACK1990	Cross-over study; fewer than 10 participants in each condition (morning light vs evening ligth)
SCHWARTZ1997	Data not extractable; fewer than 10 participants in each condition (bright light vs no light)
STEWART1990	Cross-over study; fewer than 10 participants per arm (head-mounted light vs light box)

STEWART1991	Cross-over study; fewer than 10 participants in each condition (green light vs white light)
THORELL1999	Less than 10 participants in each condition
VOLZ1990	Not SAD - non-seasonal depression
WEHR1986	Cross-over study; fewer than 10 participants in each condition (summertype light vs winter-type light)
WIRZJUSTICE1987	Cross-over study, so data not extractable; also fewer than 10 participants in each condition (bright light (> 2,500 lux): 0.5 hours vs 2 hours)
WIRZJUSTICE1993	Protocol changes part way through trial
WIRZJUSTICE1996	Not randomly assigned to different conditions
ZOU2005A	Not SAD - elderly depression inpatients

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Non-light therapy interventions for depression with a seasonal pattern/SAD

Comparisons Included in this Clinical Question

Fluoxetine v placebo
LAM1995

High ion density v low density
TERMAN1995

Moclobemide v fluoxetine
PARTONEN1996

Moclobemide v placebo
LINGJAERDE1993

Relapse Prevention: propranolol vs placebo
SCHLAGER1994

Sertraline v placebo
MOSCOVITCH2004

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
LAM1995 Study Type: RCT Type of Analysis: ITT: LOCF Blindness: No mention Duration (days): Mean 35 Setting: Outpatients; Canada Notes: RANDOMISATION: no details	n= 68 Age: Mean 36 Sex: 23 males 45 females Diagnosis: Recurrent MDD episodes with a seasonal pattern by DSM-III-R Exclusions: Satisfying neither: score =/>15 on first 17 items of HAMD-21 or score =/>12 on first 17 items of HAMD-21 and score =/>23 on HAMD-29; pregnancy or lactation; convulsions or non-stabilised serious medical illness; serious active suicide risk; DSM-III-R diagnosis of organic mental disorder, substance use disorder, schizophrenia, paranoid or delusional disorder, other psychotic disorder, panic disorder, GAD not concurrent with MDD, bipolar type I; use of other psychotropic drugs; previous use of fluoxetine; use of heterocyclic antidepressants in past 7 days or MAOI in past 14 days; concurrent use of light therapy or formal psychotherapy. Notes: 1 week placebo washout n= 86 enrolled; n= 68 after washout Baseline: BDI: Flx 21.1 (6.7); Plb 24.4 (7.1) HAMD-21: Flx 18.6 (3.9); Plb 18.9 (3.7) HAMD-29 (m): Flx 33.6 (5.8); Plb 33.3 (5.8)	**Data Used** Side effects reported Leaving treatment early due to side effects Response: 50% reduction in SIGH-SAD Response: 50% reduction in HRSD21 Response: 50% reduction in BDI SIGH-SAD mean endpoint HAMD-21 mean endpoint BDI mean endpoint	**Group 1 N= 36** Fluoxetine. Mean dose 20 mg/d **Group 2 N= 32** Placebo	Funding: Eli Lilly, Canada, Inc
LINGJAERDE1993 Study Type: RCT Type of Analysis:	n= 34 Age: Mean 43 Sex: 9 males 25 females Diagnosis:	**Data Used** Leaving treatment early due to side effects Leaving treatment early for any reason MADRS	**Group 1 N= 16** Moclobemide. Mean dose 400 mg/d **Group 2 N= 18**	Funding: unclear

completers Blindness: Double blind Duration (days): Mean 21 Setting: Outpatients; Norway Notes: RANDOMISATION: no details	mood disorder with seasonal pattern by DSM-III-R SAD by Rosenthal criteria subsyndromal SAD by Kasper criteria Exclusions: Not at least moderate depression on CGI; not considered on clinical grounds to be in need of treatment for winter depression; psychotic symptoms or suicidal ideas; serious somatic disorder; active anitdepressant treatment during past 2 weeks; pregnancy or possibility of becoming pregnant during treatment period. Notes: After acute phsae non-responders swicthed to open moclobemide. Acute phase only extracted here. Baseline: MADRS: Moclobemide 38 (9); Plb 32 (8)	(extended) mean endpoint **Data Not Used** CGI - not relevant Atypical - not relevant	Placebo	
MOSCOVITCH2004 Study Type: RCT Type of Analysis: 'ITT': minimum 1 post- baseline evaluation Blindness: Double blind Duration (days): Mean 56 Setting: Outpatients; International Notes: RANDOMISATION: computer generated	n= 187 Age: Mean 40 Sex: 42 males 145 females Diagnosis: 79% Maj dep (single or recurrent)with seasonal pattern by DSM-III-R 13% Depressive disorder NOS with seasonal pattern by DSM-III-R 7% Bipolar disorder depressed with seasonal pattern by DSM-III-R 2% Bipolar Disorder NOS with seasonal pattern by DSM-III-R Exclusions: Score <12 on HAMD-21; score <10 on 8 supplementary items for SAD evaluation; >25% improvement in placebo washout; treatment with psychoactive agent or any drug likely to interact with trial drug; suicide risk; history of alcoholism, drug misuse, poor motivation or other emotional or intellectual problems likely to invalidate informed consent or limit ability to comply with protocol. Notes: Varibale length placebo washout Baseline: HAMD-29: Srtl 36.32 (6.46); Plb 35.01 (6.56) HAMD-21: Srtl 21.11 (5.21); Plb 20.07 (5.4) HAMD-17: Srtl 18.62 (4.73); Plb 17.76 (4.92)	**Data Used** Side effects reported Leaving treatment early due to side effects Leaving treatment early for any reason Response: 50% reduction in SIGH-SAD HAMD-17 mean change HAMD-21 mean change SIGH-SAD (HAMD-29) mean change **Data Not Used** HAM-A - not relevant CGI - not relevant HAM-D - not relevant	**Group 1 N= 93** Sertraline. Mean dose 50 mg/d - 200 mg/d **Group 2 N= 94** Placebo	Funding: Supported by grants from Pfizer International Inc.; Dr Lane was formerly an employee of Pfizer Pharmaceuticals.
PARTONEN1996 Study Type: RCT	n= 32	**Data Used**	**Group 1 N= 11**	Funding: unclear

Type of Analysis: Completers Blindness: Double blind Duration (days): Mean 42 Setting: Unclear; Finland Notes: RANDOMISATION: no details	Age: Mean 44 Sex: 11 males 21 females Diagnosis: 100% Depressive disorder by DSM-III-R 18% mood disorder with seasonal pattern by DSM-III-R Exclusions: Score <16 on HAMD-17; severe suicidality; psychotic symptoms; alcohol or drug misuse; epilepsy or severe somatic disease. Notes: 5 day washout if already on antidepressant At randomisation n=209; data only available for n=183 completers; data extracted here only for n=32 with SAD Baseline: HAMD-17: Moclobemide 22.9 (3.65); Flx 22.7 (3.82) MADRS: Moclobemide 33.8 (3.32); Flx 33.0 (2.97)	MADRS mean endpoint HAMD-17 mean endpoint **Data Not Used** Medical Outcomes Study (MOS) - not relevant CGI - not relevant Response: 50% reduction in HAMD-17 - n at randomisation unclear Remission: HAMD-17 < 7 - n at randomisation unclear Leaving treatment early for any reason - n at randomisation unclear	Moclobemide. Mean dose 300 mg/d - 450 mg/d **Group 2 N= 21** Fluoxetine. Mean dose 20 mg/d - 40 mg/d	
SCHLAGER1994 Study Type: RCT Study Description: Open treatment phase with responders going on to double blind continuation phase Type of Analysis: Completers: 1 droupout not included in analysis Blindness: Double blind Duration (days): Mean 14 Setting: Unclear; US Notes: RANDOMISATION: no details	n= 23 Age: Sex: Diagnosis: 100% Recurrent MDD episodes with a seasonal pattern by DSM-III-R Exclusions: Non-repsonders to initial open treatment phase; HAMD-21<12; HAMD-21<8 and HAMD-SAD version<18 Baseline: (before open treatment phase; n=33): HAMD-21 14.8 (3.6)	**Data Used** HRSD-SAD mean endpoint Leaving treatment early for any reason **Data Not Used** Response: 50% reduction in HRSD21 - no dat	**Group 1 N= 13** Propanolol. Mean dose 33.2 mg/d **Group 2 N= 11** Placebo	Funding: unclear
TERMAN1995 Study Type: RCT Type of Analysis: Unclear Blindness: Double blind	n= 25 Age: Mean 38 Sex: 3 males 22 females Diagnosis: SAD by Rosenthal criteria major depressive episode with seasonal pattern	**Data Used** Response: 50% reduction in SIGH-SAD **Data Not Used** CGI - not relevant SIGH-SAD mean endpoint - not extractable HRSD 21 mean	**Group 1 N= 12** High density negative ions. Mean dose 30 minute sessions **Group 2 N= 13** Low density negative ions. Mean dose 30 minute sessions	Funding: National Institute of Mental Health Grant

Duration (days): Mean 20 Setting: Unclear; US Notes: RANDOMISATION: no details	by DSM-III-R Bipolar Disorder NOS with seasonal pattern by DSM-III-R Exclusions: <2 weeks baseline depressed mood in fall or winter; symptomatic in spring or summer; other DSM-III-R axis I disorder or potentially complicating illness; experience with light or negative ion treatment; taking psychotropic medication; score <20 on SIGH-SAD; score <10 on HAMD-21; score <5 on Atypical-8 Notes: 7-14 day withdrawal Baseline: Not extractable	endpoint - not extractable		

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
DANILENKO2008	n per group <10
OREN1994	No extractable data as n at randomisation and n used in analysis is unclear.
ROSENTHAL1988	n per group <10
TURNER2002	n per group <10; no extractable data
WIRZJUSTICE1990	n per group <10

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Relapse prevention

2004 Guideline

Characteristics of included studies

Study ID	Inclusion criteria	Participants	Treatment before Rz	Criteria to enter Rz	Interventions	Outcomes	Notes
Alexopoulous 2000	RDC & DSM-IV unipolar major depression without psychotic	Age: 65. Outpatients.	Open treatment with Nortriptyline (no dose given, plasma levels 60-150ng/mL) once remission	No relapse in continuation phase.	2 years on: Nortriptyline Placebo	Remission (no longer meeting RDC criteria for depression and	Study designed to investigate the relationship between

	features, HRSD-24≥19		achieved further 16 weeks continuation treatment.			HRSD≥10 for 3 weeks. Relapse (meeting RDC and DSM- IV for major depression and HRSD≥17). Executive dysfunction and memory assessed using the Dementia Rating Scale	executive and memory impairment to relapse of depression.
Bauer2000	DSM-III-R major depressive episode and HRSD-21≥15	Age: mean=47.4. Inpatients (25) and outpatients (5). N=30 (patient with unipolar depression: n=27).	Antidepressant treatment for at least 4 weeks, non-responders received adjunctive lithium for 6 weeks	Remission (HRSD≥10, CGI≤3, CGI-I 2 or 3)	4 months on 1. AD + lithium or 2 AD + placebo	Relapse (meeting criteria for DSM-III-R major depressive episode and HRSD-21≥15)	
Doogan1992	DSM-III major depressive disorder and HRSD-17≥17	Age: 18-70.	8 weeks open treatment with sertraline (50mg up 200mg, mean < 100mg)	CGI-I very much or much improved	44 weeks of: 1. Sertraline (50- 200mg, mean=69.3mg) 2. Placebo	Relapse (HRSD≥17)	≤9% patients with bipolar depression
Feiger1999	DSM-III-R non-psychotic major depression and HRSD≥20	N=131. Age: 18+. Outpatients.	16 weeks treatment with nefazodone (100-600mg)	Completers with a response (HRSD≤10 on 2 consecutive visits between weeks 6 and 10 with no 2 consecutive scores of HRSD>10 and with HRSD≤10 at weeks 15 and 16	36 weeks on: 1. Nefazodone (mean=412-438mg) 2. Placebo	Relapse (HRSD≥18 on 2 consecutive visits or early discontinuation due to lack of efficacy)	Paper gives overall results and for two relapse criteria separately.
Frank1990	RDC major depressive episode	N=230. Age: 21-65. (33 [14.3%] with bipolar II disorder)	.Imipramine (150-300mg) and interpersonal therapy (IPT) for at least 3 weeks; those in remission for 3 weeks then continued therapy for 17 weeks.	Maintenance of remission (HRSD≤7 and Raskin ≤5 for 20 weeks.	3 years of: 1. IPT 2. IPT + imipramine 3. IPT + placebo 4. Medication clinic + imipramine 5. Medication clinic + placebo	Recurrence (on 2 successive assessments: meeting RDC criteria for MDD and HRSD≥15 and Raskin ≥7)	Geddes used data from 2 and 3
Georgotas 1989	RDC unipolar major depression and HRSD-21≥16	Age: 55+, mean=64/65.6. N=52. Outpatients.	Random allocation to: 1. Phenelzine (mean=53.9mg) 2. Nortriptyline	Free from illness for 4 months and sustain HRSD≤10 for 2 months.	1 year of: 1. Phenelzine 2. Nortriptyline	Recurrence (meeting RDC criteria and HRSD≥16)	Patients on phenelzine continued treat-ment in main-tenance phase

			(mean=79mg) or 3.placebo for 7 weeks. Placebo non-responders (HRSD≥10) switched to 1 or 2 for a further 2 weeks. Responders (HRSD≤ 10) continued treatment on 1 or 2 for 4 months.		3. Placebo		unless randomimised to placebo; same with nortriptyline. No doses specified for maintenance phase, plasma levels of nortriptyline kept between 190 and 684 nmol/L, mean=407.5 and platelet MAO inhibition in phenelzine treated patients: > 70%, mean=73.8%
Gilaberte2001	DSM-III-R unipolar major depression, HRSD-17≥18 and CGI severity ≥4	N=140.Age: 18-65. Outpatients.	8 weeks open label fluoxetine (20-40mg), remitters continued with treatment for further 6 months	Remission (no longer meeting DSM-III-R for major depression and HRSD≤8 and CGI≤2)	48 weeks of: 1. Fluoxetine (20mg) 2. Placebo	Recurrence (meeting DSM-III-R criteria for major depression, HRSD≥18 and CGI ≥4)	
Hochstrasser 2001	DSM-IV unipolar recurrent major depressive episode and MADRS≥22	N=269. Age: 18-65. Inpatients and outpatients.	6-9 weeks of open treatment with citalopram (20-60mg). Responders continued treatment for further 16 weeks.	Response (MADRS≤11)	48 weeks on: 1. Citalopram (20-60mg) or 2. Placebo	Recurrence (MADRS≥22, confirmed after 3-7 days.	
Keller1998	DSM-III-R chronic major depression (lasting ≥2years) or major depression + dysthymia and HRSD- 24≥18	N=161. Age: 18-65. Outpatients.	Patients randomised to 12 weeks' treatment with 1. Sertraline or 2. Imipramine. Sertraline patients in full remission (HRSD≤7) or with a response (≥50% decrease in HRSD and HRSD≤15) entered continuation phase: 4 months further treatment with sertraline (mean=141.6mg).	Sustained response (≥50% decrease in HRSD and HRSD≤15) throughout continuation phase.	76 weeks on: 1. Sertraline (mean=141.6mg) 2. Placebo	Recurrence (at 2 weekly visits: DSM-III-R major depression for ≥3 weeks and CGI severity ≥4 and CGI-I≥3 and ≥4 point increase on HRSD)	Also gives data for re-emergence of depression by consensus assessment.
Kishimoto 1994	DSM-III major depression	N=26. Age: ≤70.	TCAs (dose not given) or mianserin (mean=29+-9mg)	In remission (HRSD≤9 for at least 3 months)	18 months of: 1. Mianserin (mean=24-26mg) or 2. Placebo	Recurrence (HRSD≥10)	At least 10/26 patients were treated initially with mianserin at a (mean)

							inadequate dose.
Klysner2002	DSM-IV unipolar major depression and MADRS≥22	N=121. Age: 65+. Outpatients. 85% in first episode.	8 weeks treatment with citalopram (20mg). Patients with MADRS≤11 continued for further 16 weeks on citalopram (20-40mg)	MADRS≤11	48 weeks on: 1. Citalopram (20-40mg) or 2. Placebo	Recurrence (MADRS≥22 confirmed after 3-7 days)	
Montgomery 1988	DSM-III major depression and HRSD>18	N=220.	6 weeks treatment with Fluoxetine (40-80mg). Responders(HRSD<12) continued on fluoxetine (40mg) for further 18 weeks.	HRSD≤8	1 year on: 1. Fluoxetine (40mg) 2. Placebo	Recurrence (HRSD>18)	Recurrence rate give for completers only. Does not specify whether any dropouts suffered a recurrence.
Montgomery 1993	DSM-III-R unipolar major depression and HRSD-21≥18	N=135. Age: 18-65. Outpatients.	8 weeks treatment with paroxetine (20-40mg)	Response (HRSD≤8)	1 year on: 1. Paroxetine (20-30mg) or 2. Placebo	Reappearance (clinical judgement or CGI worsening 2 points or CGI≥4 or deterioration for ≥7 days or DSM-III-R major depression)	Used data for DSM-III-R relapse criteria only.
Prien1984	RDC primary major depressive disorder or manic disorder.	N=150. Age: 21-60. Inpatients or outpatients	Patient treated according to clinician (AD, AD + lithium, lithium, neuropleptic or ECT) until acute symptoms were controlled. Then patients received lithium (0.6-0.9 mEq/L) + imipramine (75-150mg) for ≥2 months.	On stable dose (imipramine ≥75mg, lithium serum level of 0.6 mEq/L) for ≥2 months and GAS≥60 and RSMD total depression score≤7	2 years on: 1. Lithium 2. Imipramine (mean=137mg) 3. Lithium + imipramine 4. Placebo	Recurrence (met RDC criteria for definite major depressive disorder).	Bipolar patients randomised and analysed separately. Data not used in this review.
Reimherr 1998	DSM-III-R major depression and HRSD- 17≥16	N=395. Age: 18-65. Outpatients.	12-14 weeks' treatment with fluoxetine (20mg)	Remission (no longer meeting DSM-III-R criteria and HRSD<7 for 3 weeks)	1. Placebo for 50 weeks, 2. Fluoxetine for 50 weeks, 3. Fluoxetine for 14 weeks then placebo for 38 weeks, or 4. Fluoxetine for 38 weeks then placebo for 14 weeks	Relapse (met DSM-III-R criteria for 2 weeks or HRSD>14 for 3 weeks)	Randomised phase includes ≤12.4% bipolar patients. Extracted data for 1 and 2 only.
Robert1995	DSM-III-R major depression and MADRS≥25	N=226. Age: 19-70.	8 weeks treatment with citalopram (20-60mg)	Response (MADRS≤12)	24 weeks on: 1. Citalopram (20-60mg) or 2. Placebo	Relapse (MADRS≥25 and clinical judgement)	
Robinson	RDC major	N=47. Age: 18+.	6-13 weeks treatment with	HRSD<10 for ≥16	2 years on:	Relapse (recurrence	Collapsed data

1991	depressive episode and HRSD- 17≥18	Outpatients.	phenelzine (1mg/kg). Responders (HRSD<10) continued treatment for 16 weeks.	weeks	1.Phenelzine (60mg), 2. Phenelzine (45mg) or 3. Placebo	of depression symptoms within 3 months of randomisation. Recurrence (return of depressive symptoms after 3 months of randomised treatment.)	from groups 1 and 2
Schmidt2000	DSM-IV non-psychotic major depressive disorder, HRSD-17≥18 and CGI≥4	N=501. Age: 18-80. Outpatients.	13 weeks open treatment with fluoxetine (20mg)	Response (no longer meeting DSM criteria for major depressive disorder, HRSD≤9 and CGI≤2)	25 weeks of: 1.Fluoxetine (20mg) 2. Fluoxetine (90mg once weekly) 3. Placebo	Relapse (meeting criteria for major depressive episode and CGI ≥2)	Used data from 1 and 3 only
Terra1998	DSM-III-R moderate to severe major depressive episode without psychotic symptoms and MADRS>25 and ≥2 episodes in last 5 years	N=204. Age: 18-70.	6 weeks' treatment with fluvoxamine (100-300mg). Responders (MADRS<10 and CGI severity 1 or 2) continued with treatment for 18 weeks	Sustained response (MADRS<12 for 18 weeks)	1 year on: Fluvoxamine (100mg) Placebo	Recurrence (5 symptoms of DSM-III-R criteria for major depression at 2 visits over 8 days [or attempted/completed suicide])	
Thase2001	DSM-IV major depressive disorder and HRSD-17≥18	N=156. Age: 18+. Setting unclear.	8-12 weeks treatment with mirtazapine (15-45mg, mean=30.6mg)	Remission (HRSD≤7 and CGI-I 1 or 2)	40 weeks on: 1. Mirtazapine (15-45mg) or 2. Placebo	Relapse (HRSD≥18 or HRSD≥15 at 2 consecutive visits)	
Versiani1999	DSM-III-R major depressive disorder	N=283.Age: 18-65. Inpatients and outpatients.	6 weeks' treatment with reboxetine (8mg)	Response (≥50% decrease in HRSD- 21)	46 weeks on: 1. Reboxetine (8mg) 2. Placebo	Remission (HRSD≤10), relapse (≥50% increase in HRSD and/or HRSD≥18)	
Wilson2003	DSM-III-R major depressive disorder and HRSD-17≥18	N=113. Age: 65+, mean=77.7. Primary care patients. 72% first episode.	8 weeks' open treatment with sertraline (20-200mg), responders(≥50% decrease in HRSD score) received continuation treatment for 16-20 weeks	HRSD≤10 for 4 consecutive weeks	2 years of: Sertraline (50-100mg) Placebo	Recurrence (HRSD≥13 and meeting DSM-III-R criteria for major depressive disorder.	

Characteristics of excluded studies

Study	Reason for exclusion
Bialos1982	Inadequate definition of relapse 'appearance of a depressive episode as decided upon by the patients and the research clinician'
Burke2000	Inadequate diagnosis of depression
Coppen1978	Inadequate diagnosis of depression

Davidson1984	Inadequate definition of relapse 'clinical judgement that the patient was symptomatic enough to warrant a change in treatment or HRSD≥20'
Eric1991	Inadequate definition of relapse: not defined
Glen1984	Inadequate definition of relapse: 'an affective episode of sufficient severity to require a change in treatment'
Harrison1986	43% patients were diagnosed with dysthymia
Jenkins1990	Not a relevant comparison: maintenance treatment with gepirone
Kane1982 Y O S	Unclear description of study, only 6 unipolar patients per treatment group
Klerman1974	Inadequate definition of relapse: not defined
Kocsis1996	At least 30% patients were diagnosed with dysthymia
Lendresse1985	Inadequate definition of relapse: not defined
Mindham1972	Inadequate diagnosis of depression
Old1993	Inadequate definition of relapse: MADRS>10 or clinical judgement
Reynolds1999	43% patients were receiving adjunctive pharmacotherapy
Rouillon1989	43% of patients were diagnosed with dysthymia
Rouillon2000	Not a relevant comparison: maintenance treatment with milnacipran
Stein1980	Inadequate definition of relapse: 'deterioration over 1-2 weeks following an increase in dosage'

2009 Guideline

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
Lauritzen1996 Study Type: RCT Study Description: 2 separate continuation trials following ECT and antidepressant treatment. Trial A: imipramine vs. paroxetine, and Trial B: paroxetine vs. placebo. Blindness: Double blind Duration (days): Mean 144 Setting: Outpatients at 3 separate hospitals; Denmark. Notes: Randomised: no details. Info on Screening Process: Unknown.	n= 74 Age: Mean 59 Sex: 19 males 55 females Diagnosis: 100% Major depressive disorder by DSM-III-R Exclusions: Severe cardiovascular disease within the preceding 6 months including intraventricular conduction abnormalities, severe unstabilised somatic diseases, untreated glaucoma, dementia (MMSE score <24), schizophrenia, chronic alcohol/drug misuse, treatment with irreversible monoamine oxidase inhibitors within the preceding 14 days, pregnancy/nursing mothers, epilepsy and prophylactic lithium treatment. Notes: Patients with electrocardiological impairment were entered into trial A, and those	**Data Used** Relapse	**Group 1 N= 21** Paroxetine. Mean dose 28.5 mg/day - 20- 60 mg/day **Group 2 N= 22** Imipramine. Mean dose 138 mg/day - 100- 300 mg/day	Funding; pharma (SmithKline Beecham, London and Novo Nordisk, Copenhagen).

	without impairment were entered into trial B post-ECT acute phase. Looked at trial A only. Baseline: Group A Paroxetine Imipramine HAM-D post-ECT 9.6 (5.6) 6.6 (4.1)			
Sackeim2001 Study Type: RCT Study Description: RCT for remitters following open-label ECT Blindness: Double blind Duration (days): Mean 168 Setting: US; referrals for ECT (probably inpatients) Notes: RANDOMISATION: randomly permuted block procedure stratified as follows: psychotic, medication-resistant non-psychotic; non- psychotic + non-resistant Info on Screening Process: 349 screened for ECT; 316 entered open-label ECT phase; 159 remitted; 75 dropped out; 84 randomised	n= 84 Age: Mean 57 Sex: 28 males 56 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: Entry to phase I: HAMD-24 < 21; history of bipolar disorder, schizophrenia, schizoaffective disorder, nonmood disorder psychosis, neurological illness, alcohol or drug misuse in past year; ECT in past 6 months; severe medical illness that markedly increased risks of ECT; contraindications to study drugs Notes: 42% had psychotic features; 48% treatment resistant; Entry to RCT based on achieving remission (H-24 < 10 on 2 consecutive visits + H-24 baseline reduced by 60%); 39% had psychotic features; average 2.5 previous episodes Baseline: Entry to phase II: HAMD-24 (SD) pbo 5 (2.7); nort 5.6 (3.1) ; nort + li 6 (3.1)	**Data Used** Relapse Notes: Relapse: 2 consecutive HAMD-24 scores >= 16 + >= 10-point increase in baseline Phase II score; or CGI considerably worsened for 2 consecutive visits; or psychiatric hospitalisation because of suicidality, psychosis or significant reduction in functioning	**Group 1 N= 27** Nortripytline. Mean dose 89.9 (38.2) ng/mL - Dose adjusted to achieve between 75 and 125 ng/mL Placebo **Group 2 N= 28** Nortripytline. Mean dose 89.2 (32.2) ng/mL - Dose adjusted to achieve between 75 and 125 ng/mL Lithium. Mean dose 0.59 (0.2) mEq/L - Dose adjusted to achieve 0.5 to 0.9 mEq/L **Group 3 N= 29** Placebo - Matched both nortripytline and lithium pills	SIGN 1++; funding NIMH

References of Included Studies

Lauritzen1996 (Published Data Only)

Lauritzen, L., Odgaard, K., Clemmesen, L., et al. (1996) Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. Acta Psychiatrica Scandinavica, 94, 241-251.

Sackeim2001 (Published Data Only)

Sackeim, H. A., Haskett, R. F., Mulsant, B. H., Thase, M. E., Mann, J. J., Pettinati, H. M. et al. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA, 285, 1299-1307.

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
GORWOOD2007 Study Type: RCT Study Description: RCT followed 12 weeks' open-label escitalopram; responders entered RCT Blindness: Double blind Duration (days): Mean 168 Setting: Outpatients; Czeck Republic, France, Germany, Netherlands, Poland, Slovakia, Spain (46 sites) Notes: RANDOMISATION: computer-generated series contained in sealed opaque envelopes Info on Screening Process: 405 entered open- label phase with 333 completing treatment	n= 305 Age: Mean 73 Range 64-90 Sex: 65 males 240 females Diagnosis: 100% Major depressive disorder by DSM-IV-TR Additional specifier: Responders to acute-phase treatment Exclusions: Mean age 65; Mini-Mental State Examination < 24; current or past history of manic or hypomanic episode, schizophrenia or other psychotic disorder; mental retardation; organic mental disorders; mental disorder resulting from general medical condition; substance misuse disorder; presence or history of clinically significant neurologic disorder; neurodegenerative disorder; personality disorder likely to compromise study; suicide risk; recent/concommitant use of antipsychotics, ECT, lithium, carbemazepine, valoprate, valpromide; use of other psychotropics within week of screening Notes: Response to open-label defined as MADRS <=12 Baseline: MADRS (SD) start of RCT 5.1 (4.8); start of open- label phase 31.1 (4.7)	**Data Used** Relapse Notes: Relapse defined as MADRS >= 22 or unsatisfactory treatment effect as judged by the investigator	**Group 1 N= 152** Escitalopram. Mean dose 10 mg or 20 mg **Group 2 N= 153** Placebo	SIGN: 1++; funding Lundbeck
GRUNHAUS2001 Study Type: RCT Study Description: RCT for remitters to acute- phase ECT Blindness: Single blind Duration (days): Mean 84 Setting: Israel; patients referred for ECT following medication	n= 39 Age: Mean 60 Sex: 13 males 22 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: No specific exclusions beyond basic inclusion criteria (see setting) Notes: N male/female and other demographics based on completers; 17% psychotic features; remission	**Data Used** Relapse Notes: Relape = return of >= 5 DSM-IV symptoms of MDD + HAMD-17 >= 16	**Group 1 N= 21** Fluoxetine - 20 mg - 40 mg Melatonin - 5 mg or 10 mg **Group 2 N= 18** Fluoxetine - 20 mg - 40 mg Placebo	SIGN: 1+; funding Theodore and Vada Stanley Fuondation; fluoxetine supplied by Eli Lilly; unclear if double-blind

resistance, delusions or hallucinations, and/or very severe depression Notes: RANDOMISATION: randomised, no details Info on Screening Process: No details	defined as H-17 <= 10 and/or GAS >- 60 (5.2); fluox + pbo 26.2 (7); phase 2 7.1 (4.9); 6.8 (4.1)			
KELLNER2006 Study Type: RCT Study Description: RCT for remitters to acute- phase ECT Type of Analysis: N/A Blindness: Open Duration (days): Mean 168 Followup: None Setting: US; patients referred for ECT Notes: RANDOMISATION: random, no details Info on Screening Process: 531 entered phase I; 341 remitted with 70 relapsing and 67 dropping out during the week before the RCT; 204 available for randomisation; 201 randomised	n= 201 Age: Mean 57 Range 18-85 Sex: 65 males 136 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: Entry to phase I: HAM-D-24 < 21; schizophenia or bipolar disorder; significant CNS disease; delirium, dementia; amnestic disorder; illicit substance dependence within 12 months; general medical conditions contraindicating ECT or study medication; prior treatment failure in index episode on heterocyclic AD + lithium; ECT in past 3 months; Entry to phase II based on remission -see notes Notes: Entry to RCT based on achieving remission (H-24 < 10 on 2 consecutive visits + H-24 baseline reduced by 60%); 39% had psychotic features; average 2.2 previous episodes Baseline: HAMD-24 (SD) acute phase: 34.8 (7.2); RCT: 6.4 (2.7)	**Data Used** Relapse Notes: Relapse: 2 consecutive HAMD-24 scores >= 16 + >= 10-point increase in baseline Phase II score; or CGI considerably worsened for 2 consecutive visits; or psychiatric hospitalisation because of suicidality, psychosis or significant reduction in functioning	**Group 1 N= 98** ECT - 10 sessions over 6 months - 1-week intervals x 4, then every other week x 4; the monthly x 2 - final assessments 4 weeks after last treatment **Group 2 N= 103** Nortripytline - Mean blood serum levels at end of study 81.4 (58.5) mEq/L Lithium - Mean blood serum levels at end of study 0.53 (0.38) mEq/L	SIGN: 1+; funding NIMH
KORNSTEIN2006A Study Type: RCT Study Description: RCT for remitters to acute- phase ECT Type of Analysis: N/A Blindness: Open Duration (days): Mean 168 Followup: None Setting: US; patients referred for ECT Notes: RANDOMISATION: random, no details Info on Screening Process: 531 entered phase I; 341 remitted with 70 relapsing and 67 dropping out during the week before the RCT; 204 available for randomisation; 201 randomised	n= 201 Age: Mean 57 Range 18-85 Sex: 65 males 136 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Psychotic features Exclusions: Entry to phase I: HAM-D-24 < 21; schizophenia or bipolar disorder; significant CNS disease; delirium, dementia; amnestic disorder; illicit substance dependence within 12 months; general medical conditions contraindicating ECT or study medication; prior treatment failure in index episode on heterocyclic AD + lithium; ECT in past 3 months; Entry to phase II based on remission -see notes Notes: Entry to RCT based on achieving remission (H-24 < 10 on 2 consecutive	**Data Used** Relapse Notes: Relapse: 2 consecutive HAMD-24 scores >= 16 + >= 10-point increase in baseline Phase II score; or CGI considerably worsened for 2 consecutive visits; or psychiatric hospitalisation because of suicidality, psychosis or significant reduction in functioning	**Group 1 N= 98** ECT - 10 sessions over 6 months - 1-week intervals x 4, then every other week x 4; the monthly x 2 - final assessments 4 weeks after last treatment **Group 2 N= 103** Nortripytline - Mean blood serum levels at end of study 81.4 (58.5) mEq/L Lithium - Mean blood serum levels at end of study 0.53 (0.38) mEq/L	SIGN: 1+; funding NIMH

	visits + H-24 baseline reduced by 60%); 39% had psychotic features; average 2.2 previous episodes Baseline: HAMD-24 (SD) acute phase: 34.8 (7.2); RCT: 6.4 (2.7)			
KORNSTEIN2006A Study Type: RCT Study Description: RCT for responders to open- label acute-phase SSRI and open-label continuation phase escitalopram Blindness: Double blind Duration (days): Mean 365 Setting: Outpatients; US (28 centres) Notes: RANDOMISTION: randomised, no details Info on Screening Process: 515 entered acute- phase; 234 entered continuation phase	n= 139 Age: Mean 43 Sex: 29 males 110 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Bipolar disorder; schizophrenia or any psychotic disorder; OCD; mental retardation or any pervasive developmental or cognitive disorder; Axis I disorder other than MDD; history of pyschotic disorder; exhibited psychotic features; significant personality disorder; history of substance misuse or dependence in past 6 months; suicide risk; required concomitant psychotropic medication; pregnant or breastfeeding; women not using reliable birth control. Notes: Responders to open-label phases based on MADRS <= 12 Baseline: MADRS (SD) escitalopram 4.7 (4); placebo 4.9 (3.6)	**Data Used** Relapse Notes: Relapse defined as MADRS >= 22	**Group 1 N= 73** Escitalopram. Mean dose 15.2 mg **Group 2 N= 66** Placebo	SIGN: 1+; funding Forest Research Institute
MCGRATH2006 Study Type: RCT Study Description: RCT followed 12-week open- label fluoxetine Blindness: Double blind Duration (days): Mean 365 Setting: Unclear; US Notes: RANDOMISATION: randomised by computer-generated code for open-label phase with 570 entering treatment; 292 were considered responders of whom 262 agreed to enter RCT	n= 262 Age: Mean 38 Sex: 119 males 145 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Significant risk of suicide; pregnant or breastfeeding; women not using effective contraception; unstable physical disorder; lifetime history of any organic mental disorder, psychotic disoder, or mania; history of seizures; neurological disorder significantly affecting CNS function; active substance misusers or substance	**Data Used** Relapse Notes: Relapse defined as >=2 consecutive weeks or CGI-I of less than 'much improved' compared with ratings at baseline; relapse given as percentage, denominator unclear	**Group 1 N= 131** Fluoxetine. Mean dose 45.8 (15.1) mg **Group 2 N= 141** Placebo	SIGN: 1++; funding NIMH and NY state

	dependince in last 6 months; taking medication which may exacerbate depression; hypothyroidism without stabilisation; history of nonresponse to SSRI Notes: 23% had double depression; entry to RCT based one response defined as CGI-I score <= 2 after 2nd week of treatment Baseline: HAMD-17 4.9 (3.1)			
PERAHIA2006D Study Type: RCT Study Description: Acute phase open-label duloxetine 60 mg, then remitters randomised to duloxetine or placebo Type of Analysis: MMRM Blindness: Double blind Duration (days): Mean 182 Setting: Outpatients; Italy, France, Spain, US Notes: RANDOMISATION: randomised, no details Info on Screening Process: 681 people screened; 533 met criteria for acute-phase; 255 dropped out and 280 met criteria for randomisation to relapse prevention phase	n= 278 Age: Mean 45 Sex: 76 males 202 females Diagnosis: 100% Major depressive disorder by DSM-IV Exclusions: HAMD-17 < 18; current Axis I disorder other than MDD; anxiety disorder as a primary diagnosis within 1 year of trial; treatment-resistant depression; serious suicidal risk; serious medical illness Notes: Entry to acute phase >=1 previous episode of MDD; entry to relapse prevention phase HAMD-17 <= 9 with no diagnosis of MDD Baseline: Acute phase: HAMD-17 (SD) 23.7 (3.6); relapse prevention phase: HAMD-17 (SD) 4.9 (2.49)	**Data Used** Relapse Leaving treatment early due to lack of efficacy Leaving treatment early due to side effects Leaving treatment early for any reason Notes: Relapse = increased CGI-Severity score >= 2 points compared with end of acute phase + critria for MDD at 2 consecutive visits >= 2 weeks apart or, if 2nd visit < 2 weeks after 1st, investigator judged additional therapy required	**Group 1 N= 136** Duloxetine. Mean dose 60 mg **Group 2 N= 142** Placebo	SIGN 1+; funding Eli Lilly (code HMBC); allowed 'rescue' to duloxetine 120 mg (duloxetine group) or duloxetine 60 mg (placebo group) for those relapsing during the trial
PREVENT STUDY Study Type: RCT Study Description: Responders to acute-phase RCT randomised to 1-year maintainance after 6- month continuation (study A); responders re- randomised for year (study B) Blindness: Double blind Duration (days): Mean 365 Followup: 1 year (re-randomised) Setting: Outpatients; US, 29 sites Notes: RANDOMISATION: randomised, no details Info on Screening Process: 1096 in original RCT; 715 entered continuation phase (6 months); 336 who had been on venlafaxine randomised to study A; 131 who had been on venlafaxine randomised in study B	n= 258 Age: Mean 42 Sex: 82 males 176 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Failed to respond to fluoxetine, venlafaxine or venlafaxine XR during current episode; treatment resistant (failed >= 3 trials of >=2 classes ADs or ECT or 2 adequate trials of psychotherapy in past 3 years; known hypersensitivity to venlafaxine or fluoxetine; clinically significant heaptic, cardiovascular, renal, or other serious medical disase; seizure disorder; bipolar disorder; OCD; eating disorder;drug/alcohol dependence or misuse within 6 months; psychotic	**Data Used** Relapse Notes: Relapse defined as HAMD-17 > 12, < 50% reduction from acute baseline and meeting criteria for MDD (DSM-IV)	**Group 1 N= 129** Venlafaxine ER. Mean dose 220.8 (71.8) mg - Study B N=43 (mean dose 213.5 (75.2) mg) **Group 2 N= 129** Placebo - Study B N=40	SIGN 1+; funding Wyeth; NOTE: only those on venlafaxine randomised at each stage

	disorder including psychotic depression; current postpartum depression; significant Axis II disorders; mental disorder due to substance or medical condition; anxiety disorder; suicidal; abnormal physical exam; cancer in past 3 years; pregnancy, breastfeeding or inadequate contraception; antipsychotic, MAOI or fluoxetine within 30 days of study. Notes: Response HAMD-17 <= 12 &<50% decrease in baseline scores, or HAMD-17 <= 7; N = efficay sample as large number of protocol violations in placebo group so discounted venlafaxine group recruited in same period (N randomised 336 in 1st study, 83 2nd study) Baseline: HAMD-17 (SD) venlafaxine ER 4.3 (3.3); placebo 4.9 (3.5)			
RAPAPORT2004 Study Type: RCT Study Description: RCT for responders to 8- week open-label escitalopram; participants previously entered RCTs of acute-phase escitalopram Blindness: Double blind Duration (days): Mean 252 Setting: Unclear; US, 53 sites Notes: RANDOMISATION: randomised, no details Info on Screening Process: 502 entered open- label phase	n= 274 Age: Mean 42 Sex: 107 males 167 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Any principal Axis I diagnosis other than MDD; history of schizohrenia or other psychotic disorder; suicide risk; concomitant psychtorpic medication; for women, pregnancy or not using reliable contraception Notes: N randomised not given, so N in efficacy sample used; responders = MADRS <= 12 Baseline: HAMD (SD) escitalopram 7.7 (4.6); placebo 6.6 (4.6)	**Data Used** Relapse Notes: Definition of relapse - MADRS >= 22	**Group 1 N= 181** Escitalopram **Group 2 N= 93** Placebo. Mean dose 10mg-20mg	SIGN 1+; funding Forest Laboratories
RAPAPORT2006A Study Type: RCT Study Description: RCT followed open-label citalopram, followed by open-label risperidone augmentation for non-responders; responders then randomised to present study Blindness: Double blind Duration (days): Mean 168 Setting: Inpatients and outpatients; US, Canada, France (57 sites)	n= 243 Age: Mean 48 Sex: 89 males 154 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Failed >=1 and <=3 ADs	**Data Used** Relapse Notes: Relapse defined as significant increases in HAMD-17 and CGI-C scores (no further definition)	**Group 1 N= 123** Citalopram. Mean dose 53.1 (10.5) mg (modal) Risperidone. Mean dose 1.2 (0.6) mg (modal) **Group 2 N= 120** Citalopram. Mean dose 53.1 (10.5) mg (modal) Placebo	SIGN: 1+; funding Janssen Pharmaceutica

Notes: RANDOMISATION: randomised, no details Info on Screening Process: 633 screened for citalopram open-label phase; 502 enrolled; 390 enrolled in open-label augmentation phase; 348 completed of whom 243 had responded	Exclusions: Dementia; bipolar disorder; borderline personality disorder; unstable medical conditions Notes: Eligible for RCT if HAMD-17 <= 7 or CGI-Severity = 1 or 2 following risperidone augmentation; 5 patients with psychotic features Baseline: HAMD-17 6 (entry to RCT)			
VAN den BROEK2006 Study Type: RCT Study Description: RCT followed response to ECT in patients with antidepressant failure Blindness: Double blind Duration (days): Mean 168 Setting: Inpatients; Holland (2 sites) Notes: RANDOMISATION: randomised, pharmacist used random number tables Info on Screening Process: 16 patients recruited from other trials; no further details	n= 27 Age: Mean 51 Sex: 7 males 20 females Diagnosis: 100% Major depressive disorder by DSM-IV Additional specifier: Responders to acute-phase treatment Exclusions: Schizophrenia; bipolar or schizoaffective disorder; organic brain syndrome; chronic alcohol or drug misuse; presence of an absoule contraindication for imipramine; pregnancy or risk of pregnancy; ECT during current episode Notes: Patients entered trial if had responded to ECT with 50% reduction in baseline HAMD scores and maximum HAMD score of 16 within 2 days of ECT and 1-week post- ECT assessment; 9 had psychotic features Baseline: HAMD-17 (SD) at entry to RCT placebo 5.9 (3.8); imipramine 4.9 (2.5)	**Data Used** Relapse Notes: Relapse defined as 'moderately worse' compared with baseline on CGI-I	**Group 1 N= 12** Imipramine. Mean dose 209 mg **Group 2 N= 15** Placebo	SIGN 1++; funding Psychiactric Hospital Parnassia, The Hague, Holland

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
SERRA2006	Very small study (< 10 in one arm) (maintenance ECT + nortriptyline vs nortriptyline following remission with ECT)

References of Included Studies

GORWOOD2007 (Unpublished and Published Data)

*Gorwood, P., Weiller, E., Lemming, O., & Katona, C. (2007). Escitalopram prevents relapse in older patients with major depressive disorder. American Journal of Geriatric Psychiatry, 15, 581-593. Lundbeck. A double-blind, randomised, placebo-controlled study of the efficacy of escitalopram in the prevention of relapse of major depressive episodes in elderly patients. Report date: 30 January 2006.

GRUNHAUS2001 (Published Data Only)

Grunhaus, L., Hirschman, S., Dolberg, O. T., Schreiber, S., & Dannon, P. N. (2001). Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. Journal of ECT, 17, 124-128.

KELLNER2006 (Published Data Only)

Rasmussen, K. G., Knapp, R. G., Biggs, M. M., Smith, G. E., Rummans, T. A., Petrides, G. et al. (2007). Data management and design issues in an unmasked randomized trial of electroconvulsive therapy for relapse prevention of severe depression: the consortium for research in electroconvulsive therapy trial. Journal of ECT, 23, 244-250.

*Kellner, C. H., Knapp, R. G., Petrides, G., Rummans, T. A., Husain, M. M., Rasmussen, K. et al. (2006). Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Archives of General Psychiatry, 63, 1337-1344.

KORNSTEIN2006A (Published Data Only)

Kornstein, S. G., Bose, A., Li, D., Saikali, K. G., & Gandhi, C. (2006). Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. Journal of Clinical Psychiatry, 67, 1767-1775.

MCGRATH2006 (Published Data Only)

McGrath, P. J., Stewart, J. W., Quitkin, F. M., Chen, Y., Alpert, J. E., Nierenberg, A. A., et al. (2006). Predictors of relapse in a prospective study of fluoxetine treatment of major depression. American Journal of Psychiatry, 163, 1542-1548.

PERAHIA2006D (Published Data Only)

Eli Lilly study F1J-MC-HMBC, CT Registry ID# 4445. Duloxetine versus placebo in the prevention of relapse of major depressive disorder. Clinicaltrialresults.org [date site accessed 13.06.08] Perahia, D. G., Gilaberte, I., Wang, F., Wiltse, C. G., Huckins, S. A., Clemens, J. W. et al. (2006). Duloxetine in the prevention of relapse of major depressive disorder: double-blind placebo- controlled study. British Journal of Psychiatry, 188, 346-353.

PREVENT STUDY (Published Data Only)

Keller, M., Trivedi, M., Thase, M., Shelton, R., Kornstein, S., Nemeroff, C. et al. (2007). The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: Outcomes from the 2-year and combined maintenance phases. Journal of Clinical Psychiatry, 68, 1246-1256.

Kocsis, J., Thase, M., Trivedi, M., Shelton, R., Kornstein, S., Nemeroff, C. et al. (2007). Prevention of recurrent episodes of depression with venlafaxine ER in a 1-year maintenance phase from the PREVENT study. Journal of Clinical Psychiatry, 68, 1014-1023.

RAPAPORT2004 (Unpublished and Published Data)

Forest Laboratories Inc. Placebo-Controlled Evaluation of the Safety and Efficacy of Escitalopram in the Prevention of Depression Relapse (SCT-MD-03). Report date: October 2001.

*Rapaport, M. H., Bose, A., & Zheng, H. (2004). Escitalopram continuation treatment prevents relapse of depressive episodes. Journal of Clinical Psychiatry, 65, 44-49.

RAPAPORT2006A (Published Data Only)

Rapaport, M. H., Gharabawi, G. M., Canuso, C. M., Mahmoud, R. A., Keller, M. B., Bossie, C. A. et al. (2006). Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation.[erratum appears in Neuropsychopharmacology. 2006 Nov;31(11):2514]. Neuropsychopharmacology, 31, 2505-2513.

VAN den BROEK2006 (Published Data Only)
van, d. Broek, W.W., Birkenhager, T. K., Mulder, P. G., Bruijn, J. A., & Moleman, P. (2006). Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. Journal of Clinical Psychiatry, 67, 263-268.

References of Excluded Studies

SERRA2006 (Published Data Only)
Serra, M., Gastó, C., Navarro, V., Torres, X.,, Blanch, J. & Masana., G. (2006) Tratamiento electroconvulsivo de mantenimiento en la depresión unipolar psicótica del anciano. Med Clin (Barc), 126, 491-492.

Seasonal affective disorder

Non-light therapy interventions for depression with a seasonal pattern/SAD - relapse prevention

Comparisons Included in this Clinical Question

Bupropion XL v placebo
MODELL2005 study 1
MODELL2005 study2
MODELL2005 study3

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
MODELL2005 study 1 Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Mean 180 Followup: *see notes Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 277 Age: Mean 42 Sex: 72 males 200 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV & SCID modified for SAD Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with Bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 5 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in	**Data Used** Recurrence **Data Not Used** Leaving treatment early for any reason - not reported separately by study Leaving treatment early due to side effects - not reported separately by study Notes: 'recurrence': SIGH-SAD score =/>20 for at least 1 week (decision could also be made on 'clinical grounds' based on DSM-IV)	**Group 1 N= 142** Buspirone. Mean dose 150-300 mg/d **Group 2 N= 135** Placebo	Funding: GlaxoSmithKline

	previous 3 weeks Notes: * trial length is unclear: started Sept/Nov and continued to end March so assumed approx 6 months Baseline: N/R			
MODELL2005 study2 Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 311 Age: Mean 42 Sex: 99 males 207 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV & SCID modified for SAD Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 5 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in previous 3 weeks Baseline: N/R	**Data Used** Recurrence **Data Not Used** Leaving treatment early due to side effects - not reported separately by study Leaving treatment early for any reason - not reported separately by study	**Group 1 N= 158** Bupropion XL. Mean dose 150-300 mg/d **Group 2 N= 153** Placebo	Funding: GlaxoSmithKline
MODELL2005 study3 Study Type: RCT Type of Analysis: 'ITT' Blindness: Double blind Duration (days): Setting: Multisite; US and Canada Notes: RANDOMISATION: yes, blocked with telephone registration	n= 473 Age: Mean 41 Sex: 142 males 322 females Diagnosis: 100% History of MDD with seasonal pattern by DSM-IV Additional specifier: Score =/<7 HAMD-17 Additional specifier2: Score =/<10 HAMD-24 Exclusions: <18 years old; currently depressed at baseline or randomisation (score >7 on HAMD-17 and/or score >10 on SIGH-SAD); not clinicaly appropriate for treatment with Bupropion XL; not in general good health; pregnant or female not using reliable contraceptive; using light therapy or traveling to sunny destination > 7 days during study; medical problems; history of eating disorder, bipolar I disorder; schizophrenia or other psychotic disorder; concomitant anxiety disorder; recurrent summer depressions; recent drug or acohol misuse; treatment for depression since preceding winter or used psychoactive medication in previous 3 weeks Baseline: N/R	**Data Used** Recurrence **Data Not Used** Leaving treatment early due to side effects - not reported separately by study Leaving treatment early for any reason - not reported separately by study	**Group 1 N= 242** Bupropion XL. Mean dose 150-300 mg/d **Group 2 N= 231** Placebo	Funding: GlaxoSmithKline

References of Included Studies

MODELL2005 study 1 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.

MODELL2005 study2 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.

MODELL2005 study3 (Published Data Only)

Modell, J.G., Rosenthal, N.E., Harriet, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B. & Wightman, D.S. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion xl. Biological Psychiatry, 58, 658-667.