Augmentation with lithium - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Baumann 1996 Y I AN	Allocation: Random (no details) Duration: (1 week washout + 4 weeks open treatment) 1 week of randomised treatment (+ 1 week open treatment)	Inpatients. N=24. Aged: 18-65. Diagnosis: DSM-III single episode depressive disorder, recurrent depressive disorder, bipolar: depressed (1 patient) or dysthymic disorder (1 patient)	Phase 1: Citalopram (40mg up to 60mg) for 4 weeks. Non-responders through to phase 2. Randomisation to: 1. Lithium 800mg 2. Placebo for 1 week Phase 3: All patients received	1. HRSD mean endpoint scores 2. Non-responders (Patients not achieving ≥50% decrease in HRSD)	Planned plasma levels: 0.5-0.8mmol/L. Mean on day 1= 0.75+-0.22mmol/L, mean on day 7 =0.5+-	B

	Analysis: ITT		lithium for 1 week.		0.24mmol/L	
Bloch1997 Y O	Allocation: Random (no details) Duration: 5 weeks (+ 1 week washout) Analysis: ITT	Outpatients. N=31. Age: 26-75. Diagnosis: DSM-III-R non-psychotic major depression, non treatment-resistant, HRSD≥18. (6% patients diagnosed with bipolar disorder.)	1. Desipramine (150-300mg, median=200mg) + lithium (600mg up to 900 mg, median = 900mg) 2. Desipramine (dose as above) + placebo	1. HRSD mean endpoint scores 2. Leaving the study early due to side effects 3. Non-responders (patients not achieving ≥50% decrease in HRSD and HRSD≤16 and 'much' or 'markedly' improved on CGI) 4 Non-remitters (patients not achieving HRSD≤10) 5. Leaving the study early	Planned plasma level: 0.7-1.0mEq/L. Mean = 0.77+-0.28mEq/L	B
Cappiello 1998 Y M	Allocation: Random (no details) Duration: 5 weeks (+ 2 weeks' placebo lead in). Analysis: LOCF (≥2 weeks treatment)	Inpatients and outpatients. N=31. Age: 23-64, mean=39.8. Diagnosis: DSM-III-R major depression, HRSD≥18. (14% patients diagn-osed with bipolar disorder). 62% previously failed ≥ 1 antidepressant treatment.	1. Desipramine (median=200mg) + lithium (900mg) 2. Desipramine (as above) + placebo	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥ 50% decrease in HRSD & HRSD =10) 3. Leaving the study early 4. Leaving the study early due to side effects	Planned plasma level: 0.50-1.00mmol/L. Mean = 0.67+-0.19mmol/L, range = 0.34-0.92mmol/L	B
Januel2002 Y I	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Inpatients. N=149. Age: 18-65. Diagnosis: DSM-IV major depression, MADRS ≥25	1. Clomipramine (150mg) + lithium (750mg) 2. Clomipramine (150mg) + placebo	1. MADRS mean endpoint scores 2. Non-remitters (patients not achieving MADRS<10) 3. Leaving the study early 4. Leaving the study early due to side effects 5. Patients reporting side effects	Lithium plasma level: mean = 0.5+-0.18mmol/L. Includes unpublished data.	B
Jensen1992 E I	Allocation: Random (no details) Duration: 6 weeks (+ 1 wk washout) Analysis: LOCF	Inpatients. N=44 Age: 65+. Diagnosis: DSM-III major depressive disorder, HRSD≥15	1. Nortriptyline (25-100mg, median=75mg) + lithium (300-600, median=450mg 2. Nortriptyline (50-100mg, median =75mg) + placebo	1. Leaving the study early 2. Leaving the study early due to side effects 3. Non-remitters (patients not achieving HRSD≤8)	12-hour stand-ard serum level: median = 0.6mmol/L, range:0.5-0.7mmol/L	B
Joffe1993a Y O AN	Allocation: Random (no details) Duration: 2 weeks	Outpatients.N=51.Age: mean=37.4 Diagnosis: RDC unipolar, non-psychotic, major depression. HRSD ≥16 after 5 weeks of desipramine (N=46) or imipramine (N=5)	1. TCA + lithium (900mg) 2. TCA + placebo 3. TCA + T3 (37.5µg)	1. HRSD mean endpoint scores 2. Non-responders (patients not achieving ≥50% decrease in HRSD & HRSD ≤10)	Target plasma level: ≥0.55nmol/L. Mean = 0.68 nmol/L, range: 0.56-0.93nmol/L	B
Nierenberg 2003 Y O I TR	Allocation: Random (no details) Duration: 6 weeks Analysis: ITT	Outpatients. N=35. 16 female. Age: 18-70. Diagnosis: DSM-III-R major depressive disorder, HRSD-17≥18. Failed at least 1 but less than 5 adequate medication trials of at least 6 weeks duration each.	6 weeks open treatment with nortriptyline (100mg) non-responders randomised to: 1. Nortriptyline (100mg) + Lithium 2. Nortriptyline (100mg) + placebo	1. Non-responders (patients not achieving ≥50% decrease in HRSD-17) 2. Leaving the study early	Mean blood level at week 2 = 0.63 (range: 0.3-1.4)	B

		Mean number of failed trials = lithium: 1.9+-1.2, placebo: 2.5+-1.6				
Shahal1996 Y I	Allocation: Random (no details) Duration: 5 weeks Analysis: completer	Inpatients. N= 22. Age: mean =53 +-16 years. Diagnosis: DSM-III-R major depression without psychotic features.	1. Imipramine (150-175mg) + lithium (mean=630mg) 2. Imipramine (150-175mg) + placebo	1. Leaving the study early	Target plasma level: 0.7-0.9m Eq/L Mean = 0.8+-0.2mEq/L	B
Stein1993 Y ? AN	Allocation: Random (no details) Duration: 3 weeks Analysis: completer (no dropouts)	N= 34. Aged: 18-65. Diagnosis: RDC major depressive disorder, failure to respond to at least 3 weeks of TCA treatment, HRSD≥18	1. Lithium (250mg) 2. Placebo Phase 2 (weeks 4-6): 1. Lithium (750mg) 2. Lithium (250mg) Phase 3 (weeks 7-9): 1. Lithium (750mg) 2. Lithium (750mg) Only extracted data from phase 1.	1. HRSD mean endpoint scores 2. Leaving the study early 3. Leaving the study early due to side effects	Mean plasma level = 0.76+-0.45mmol/l	B
Zusky1988 Y ? AN	Allocation: Random (no details) Duration: 3 weeks Analysis: LOCF	N= 18. Age: 18-80. Diagnosis: DSM-III major depressive disorder without psychosis, treatment resistant (HRSD ≥12 after least 4 weeks of adequate antidepressant treatment)	1. Antidepressant + lithium (300 mg up to 900mg) 2. Antidepressant + placebo	1. HRSD mean endpoint scores 2. Non-remitters (patients not achieving HRSD≤7) 3. Leaving the study early 4. Non-responders (patients not achieving ≥50% decrease on HRSD)	Mean plasma level = 0.57+-0.18	B

Characteristics of excluded studies

Study	Reason for exclusion
Bauer1999	Not relevant comparison: lithium + amitriptyline versus lithium + paroxetine
Bauer2000	Not relevant comparison: patients who did not respond to various ADs treated with lithium, remitters randomised to continue on or switch to pbo
Browne1990	3/17 (17.65%) patients were diagnosed with bipolar depression
Bruijn1998	Not relevant comparison: lithium + imipramine versus lithium + mirtazapine
Dinan1989	Not relevant comparison: lithium + TCAs versus ECT
Fava1994 Y ? TR	Mean lithium level=0.21+-0.11meq/litre
Fava2002 Y O TR	Mean lithium level=0.37+-0.15mEq/L
Hardy1997	Not relevant comparison: patients in remission after treatment with antidepressant + lithium randomised to continue with antidepressant + lithium or switch to antidepressant + placebo
Heninger1983	Inadequate randomisation method: 'the 1st 3 to enter the study received lithium, the 2nd 3 placebo, and thereafter patients were assigned in alternating order to placebo or lithium while we attempted to balance as near possible the placebo and lithium within AD drug treatment groups'
Hoencamp1994	Not relevant comparison: lithium + maprotiline versus brofaromine + maprotiline.
Kantor1986	Inadequate description of randomisation; 6/13 patients were removed from the analyses for 'methodologic contamination'

Katona1995	Sample included patients diagnosed with bipolar depression, numbers not given
Lingjaerde1974	Inadequate diagnosis
Milijkovic1997 Y I	Not carried out under double-blind conditions
Nick1976	Inadequate diagnosis.
Reynolds1996	Not an RCT
Rybakowski1999	Not a relevant comparison: AD + lithium versus AD + carbamazepine
Schopf1989	33.3% patients were diagnosed with bipolar disorder

Augmentation with pindolol - studies in previous guideline

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	AC
Bordet 1998 Y M I	Allocation: Random (by independent centre using tables of random numbers stratified in blocks of 4). Duration: 21 days. Analysis: ITT	Inpatients and outpatients. N=100, 70 female. Age: 18-65, mean = 42. Diagnosis: DSM-IV unipolar major depressive episode (non psychotic subtype), HRSD-17≥18. 18% had 'past unsuccessful treatment of depression'. Mean baseline HRSD=24	1. Paroxetine (20mg) + pindolol (15mg for 21 days -> 10mg for 4 days -> 5mg for 3 days -> 0mg) 2. Paroxetine (20mg) + placebo	1. HRSD-17 mean endpoint scores at early assessment 2. HRSD-17 mean endpoint scores at late assessment (day 21) 3. Non-remitters at early assessment (patients not achieving HRSD≤10) 4. Non-remitters at late assessment (patients not achieving HRSD≤10) 5. Leaving the study early 6. Leaving the study early due to side effects	Carried out by 20 psychiatrists in France.	A
Maes 1999 Y I I	Allocation: Random (no details). Duration 5 weeks (+ 10 day washout). Analysis: LOCF	Inpatients. N=34. Age: 25-70. Diagnosis: DSM-III-R major depression, HRSD ≥16. 22 patients with TRD (Thase and Rush stage 1). Mean baseline scores - pindolol: HRSD-17=21.9+-4.7	1. Fluoxetine (20mg) 2. Fluoxetine (20mg) + Pindolol (7.5mg) 3. Fluoxetine (20mg) + mianserin (30mg). Data Extracted for 1 and 2	1. HRSD-17 mean change scores at late assessment 2. Non-responders at late assessment (patients not achieving ≥50% decrease in HRSD)	Conducted on a treatment resistant depression ward in a Belgian hospital.	B
Perez 1997 Y P I	Allocation: Random (in blocks of 4 by the RANLab programme in a VAX system). Duration 6 weeks (+ 1 week placebo wash-) out). Analysis: LOCF	Outpatients. N=111,79 female, aged: 18+. Diagnosis: DSM-IV unipolar major depression, HRSD-17≥18. Median baseline HRSD=21, range=18-35	1. Fluoxetine (20mg) + pindolol (7.5mg) 2. Fluoxetine (20mg) + placebo	1. HRSD-17 mean change scores at late assessment 2. Leaving the study early 3. Non-responders at last assessment (patients not achieving ≥50% decrease in HRSD) 4. Non-remitters at late assessment (patients not achieving HRSD≤8) 5. Leaving the study early due to side effects	Conducted by 4 psychiatrists in the affective disorders unit of the Sant Pau Hospital, Barcelona.	B
Perez 1999 Y O	Allocation: Random (using computer	Outpatients & 2 outpatients. N=80, aged:18-65 . Diagnosis:	All patients received fluoxetine (40mg),	1. HRSD-17 mean endpoint scores at early assessment 2. Non-responders at early assessment (patients not	Conducted by 4 psychiatrists in	B