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REVIEW

Antidepressants and their effect on sleep

Andrew G. Mayers[1,2]* and David S. Baldwin[3]

[1]*Perinatal Mental Health, University of Southampton, UK*
[2]*Faculty of Media, Arts and Society, Southampton Solent University, UK*
[3]*University Department of Psychiatry, University of Southampton, UK*

Given the relationship between sleep and depression, there is inevitably going to be an effect of antidepressants on sleep. Current evidence suggests that this effect depends on the class of antidepressant used and the dosage. The extent of variation between the effects of antidepressants and sleep may relate to their mechanism of action. This systematic review examines randomised-controlled trials (RCTs) that have reported the effect that antidepressants appear to have on sleep. RCTs are not restricted to depressed populations, since several studies provide useful information about the effects on sleep in other groups. Nevertheless, the distinction is made between those studies because the participant's health may influence the baseline sleep profiles and the effect of the antidepressant. Insomnia is often seen with monoamine oxidase inhibitors (MAOIs), with all tricyclic antidepressants (TCAs) except amitriptyline, and all selective serotonin reuptake inhibitors (SSRIs) with venlafaxine and moclobemide as well. Sedation has been reported with all TCAs except desipramine, with mirtazapine and nefazodone, the TCA-related maprotiline, trazodone and mianserin, and with all MAOIs. REM sleep suppression has been observed with all TCAs except trimipramine, but especially clomipramine, with all MAOIs and SSRIs and with venlafaxine, trazodone and bupropion. However, the effect on sleep varies between compounds within antidepressant classes, differences relating to the amount of sedative or alerting (insomnia) effects, changes to baseline sleep parameters, differences relating to REM sleep, and the degree of sleep-related side effects. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — antidepressants; sleep; review; randomised-controlled trials

REVIEW METHOD

The review exercise was undertaken by exploring the Ovid® database, searching the CINAHL (1982—May 2005), EMBASE (1980—May 2005), Ovid MEDLINE® (1966—May 2005) and PsychINFO (1985—May 2005). A search strategy was undertaken to improve the likelihood of including high quality randomised controlled-trials (RCTs) that used a double-blind randomisation of participants into groups of at least 5 (per group), included in a baseline and follow-up examination of the effect of antidepressants on sleep, where those antidepressants were compared to placebo (placebo-controlled trials) and/or to other antidepressants (comparator trials). Papers were selected regardless of the nature of the participants. Antidepressant effects on sleep may vary with the current health of the participant and it is important to make that distinction. Careful consideration is also paid to the dose of antidepressant as that may explain some of the variation between studies in similar participant groups. A more general overview is also presented on the mechanisms of action of differing classes of antidepressants that might explain the effect they appear to have on sleep.

Following exclusions, 120 papers were examined, 53 of which included placebo. Those papers are presented in Table 1. The following section presents general findings for each antidepressant class, and indicates the mechanisms that might be responsible for those effects. Within each class

* Correspondence to: Andrew Mayers, Perinatal Mental Health, The Lodge, Tatchbury Mount, Calmore, Southampton, SO40 2RZ,UK.
Tel: +44 (0)23 8087 4330. Fax: +44 (0)23 8087 4360.
E-mail: a.g.mayers@soton.ac.uk

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Table 1. Effect of antidepressants on sleep: summary of randomised controlled trials

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Amitriptyline						
Capaci and Hepguler, 2002	10–20 mg	Paroxetine 20–40 mg	Fibromyalgia patients	40	8 weeks	AMI sig improvement disturbed sleep weeks 4 and 8 ($p = 0.008$; $p < 0.001$), PAR sig improved week 8 ($p = 0.002$), AMI sig better than PAR at weeks 4 and 8 ($p = 0.002$; $p < 0.001$); AMI sig improvement non-refreshed sleep weeks 4 and 8 ($p = 0.008$; $p < 0.001$), PAR sig improved week 8 ($p = 0.031$), AMI sig better than PAR week 8 ($p = 0.011$)
Mercadante *et al.*, 2002	25–50 mg	Placebo	Cancer patients	16	2 weeks	Drowsiness sig more intense with AMI vs PLC ($p = 0.036$)
Raigrodski *et al.*, 2001	25 mg/night	Placebo	Bruxism patients	10	4 weeks	AMI did not increase TST or reduce EMG activity, compared to PLC
Hindmarch *et al.*, 2000	50 mg	Milnacipran 75 mg Placebo	Healthy volunteers	10	3 days	AMI group showed sig increases in subjective ratings of sedation and difficulty waking ($p < 0.05$), compared to PLC; MIL not different to PLC
Versiani *et al.*, 1999	50–250 mg	Fluoxetine 20 mg	Depressed patients	157	8 weeks	HAMDS reduced with both drugs, but sig more for AMI (−3.3) than FLX (−1.9; $p < 0.001$); daytime somnolence reported sig more often AMI (40.0%) than FLX (14.3%; $p < 0.001$)
Hannonen *et al.*, 1998	25–37.5 mg	1: Moclobemide 450–600 mg; 2: Placebo	Fibromyalgia patients	130	12 weeks	AMI sig improvement subjective sleep ($p < 0.001$) and fatigue ($p < 0.01$); MOC group no improvement, but PLC group also showed improvement in these ratings ($p < 0.05$)
Moller *et al.*, 1998	75–225 mg	Sertraline 50–150 mg	Depressed patients	160	6 weeks	AMI sig better improvements in HAMDS than SER (AMI −2.4; SER −1.8; $p = 0.008$)
Rosenzweig *et al.*, 1998	50 mg	1: Befloxatone 10 mg 2: Placebo	Elderly (65–85) healthy volunteers	12	3 days	AMI worsened subjective alertness (poorer ease of waking, $p = 0.002$; poorer behaviour following waking, $p = 0.009$—suggesting 'hang-over' effect); BEF maintained alertness; no other subjective sleep variables affected
Srisurapanont, 1998	Mean 57.7 mg	Lorazepam (mean) 2.1 mg	Opiate withdrawal patients	27	5 days	No difference between drugs on LSEQ ratings, except ease of waking (AMI 132.8, LOR 167.6; $p = 0.047$), suggesting poorer subjective waking for AMI
Mertz *et al.*, 1998	50 mg/night	Placebo	Gastric patients	14	4 weeks	AMI poorer SE, increased arousal and reduced REM sleep, compared to PLC (no SWS)
De Ronchi *et al.*, 1998	50–100 mg	Fluoxetine 20 mg	Depressed patients	65	10 weeks	LSEQ sig increased for AMI (94.7) and FLX (108.6), no between-group differences
Koh, 1997	30 mg/night	Placebo	Rheumatic patients	100	2 weeks	AMI group showed sig improvements in restful sleep, compared to PLC ($p < 0.001$)
Kasper, 1997	Mean 21.6–49.4 mg	Mirtazapine (mean) 94.2–180.1 mg	Depressed patients	405	5–6 weeks	No difference on HAMDS between drugs, but both showed decrease (AMI: 4.90 vs 1.74; MIR: 4.80 vs 1.66; within-group significance not reported)
Ataoglu, 1997	50 mg	Paroxetine 20 mg	Fibromyalgia patients	68	6 weeks	Self-reported sleep perceptions improved at days 15, 30 and 45 for PAR ($p < 0.01$) and days 30 and 45 for AMI ($p < 0.01$); no between-group differences
Staner *et al.*, 1995	150 mg	Paroxetine 30 mg	Depressed patients	40	4 weeks	Both drugs reduced REM sleep, but only PAR demonstrated an alerting effect

Carette *et al.*, 1995	25 mg	Placebo	Fibromyalgia patients	22	8 weeks	Groups only investigated in respect of Non-REM parameters; neither group presented changes in non-REM after treatment
Robbe and Hanlon, 1995	See paroxetine; AMI = active control in this pct					
Casper *et al.*, 1994	100–250 mg	Imipramine 100–250 mg	Depressed patients	79	6 weeks	Sig greater improvement in EMA and WASO for AMI, compared to IMI, weeks 2 ($p = 0.008$), 3 ($p = 0.009$) and 4 ($p = 0.04$); improvements earlier for AMI than IMI, but only in treatment responders; both groups reported less SL, EMA and WASO week 1, regardless of treatment response ($p < 0.001$), only responders continued improvement by week 4 ($p = 0.003$)
Kerrick *et al.*, 1993	50 mg	Placebo	Hip or knee arthroplasty patients	28	3 days	AMI or PLC used as adjunct to opiods in 3-day postop following arthroplasty; SL ratings sig better in AMI group, compared to PLC ($p < 0.025$)
Kerr *et al.*, 1993	75 mg	Fluoxetine 20 mg	Elderly depressed patients	66	7 weeks	LSEQ scores improved both groups; AMI sig shorter SL week 1 than FLX ($p < 0.05$), no other between-group differences (including no sig rating of 'hangover' for AMI, despite quick sedation at week 1); however, LARS scores indicated that FLX patients less drowsy than AMI at weeks 1 and 2 ($p < 0.05$)
Kerkhofs *et al.*, 1990	150 mg	Fluoxetine 60 mg	Depressed patients	34	6 weeks	Both groups sig decrease REM% ($p < 0.001$) and increase in REML ($p < 0.001$), but no between-group differences
Zitman *et al.*, 1990	75 mg	Placebo	Chronic pain patients	39	12 weeks	AMI group 'slept better' from second week, compared to PLC; AMI pts slept for longer than PLC pts, sig so at week 2 ($p < 0.01$)
Hubain, 1990	100–225 mg	Alprazolam 4–9 mg	Severely depressed	30	6 weeks	Both groups showed lengthened REML, and less REM time
Ventafridda, 1988	25–75 mg	Trazodone 75–225 mg	Chronic pain patients	45	15 days	Both groups showed increase in TST (approx 2 h per day; ns), but actual time in bed was sig more reduced in TRZ (4 h) than AMI (1.5; $p = 0.005$)
Blacker *et al.*, 1988	See trazodone, the main focus of this paper					
Skrumsager, 1986	150 mg	Femoxetine 600 mg	Depressed patients	81	6 weeks	AMI group showed sig reduction in HAMDS; no such change with femoxetine
Shipley *et al.*, 1985	See Desipramine, the main focus of this paper					
Clomipramine						
Lepine *et al.*, 2000	50–150 mg	Sertraline 50–200 mg	Depressed outpatients	166	8 weeks	LSEQ items sig increased from baseline in both groups ($p < 0.001$), but no sig between-group differences; HAMDS sig reduced for both groups (p value not specified), but no sig between groups differences
Eberhard *et al.*, 1988	25–150 mg	Maprotiline 50–150 mg	Depressed patients	52	6 weeks	Sig improvement both groups sleep disturbance ($p < 0.01$); no between-group differences
Lacey *et al.*, 1977	25–75 mg	Placebo	Healthy volunteers	12	4 nights × 2	Randomly assigned to PLC then CLO 6 weeks later, or CLO then PLC; CLO nights slightly more WMINS than PLC (ns); CLO nights sig less REM% ($p < 0.001$) than PLC (REM almost totally suppressed with CLO)

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Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Imipramine						
Volkers *et al.*, 2002	Mean 220 mg	Fluvoxamine (mean) 201 mg	Depressed patients	52	4 weeks	IMI more fragmentation of motor activity during sleep ($p < 0.05$) than FLUV
Bruijn *et al.*, 1999	Mean 235 mg	Mirtazapine (mean) 77 mg	Depressed inpatients	107	4 weeks	MIR rapid improvements in sleep week 2, normalising by week 4; IMI more gradual improvement, exceeding MIR by week 4
Volz, 1997	100–150 mg	Brofaromine 100–150 mg	Depressed patients	198	6 weeks	Both groups similar reductions HAMDS (IMI: 2.44/−1.16; BRO: 2.16/−1.46; ns)
Sonntag *et al.*, 1996	50–200 mg	Trimipramine 50–250 mg	Depressed inpatients (male)	20	4 weeks	TRIM sig increased TST, after 4 weeks, sig reduced WMINS immediately and through to 4 weeks, sig increased REM time immediately and through to 4 weeks, sig reduced REML immediately, but increased again to 4 weeks (ns); IMI sig increased SL by end of 4 weeks, sig increased stage 1 sleep immediately and through to 4 weeks, sig reduced REM time immediately, but sig increased again to 4 weeks, sig increased REML immediately, but sig reduced this again to 4 weeks; no *p* values stated
Van Laar, 1995	See nefazodone					
Rosenberg, 1994	50–150 mg	1. Citalopram 10–30 mg 2. Citalopram 20–60 mg	Depressed patients in primary care	472	6 weeks	All groups showed reduction in HAMDS, but not sig between groups
Cassano *et al.*, 1994	25–250 mg	1: Alprazolam 1–10 mg 2: Placebo	Panic/agoraphobia patients	1168	8 weeks	Sig more sedation for ALP (58%) than IMI (31%) or PLC (21%); sig more insomnia for IMI (22%) than ALP (3%) and PLC (12%)
Ware *et al.*, 1989	75–200 mg	Trimipramine 75–200 mg	Depressed patients presenting insomnia	30	4 weeks	Both groups reported shorter SL initially, but IMI increasing SL after 7 days, TRIM continued improving; TST increased TRIM, but decreased IMI ($p = 0.02$), TST and SE sig improved for TRIM ($p < 0.01$), WASO greater for IMI than TRIM ($p < 0.01$), REML sig increased for IMI, TRIM no change, REM% sig decreased for IMI ($p < 0.01$), TRIM no change
Trimipramine						
Riemann *et al.*, 2002	Mean 100 mg	1: Lormetazepam 2: Placebo	Insomnia patients	55	4 weeks	TRIM did not suppress REM sleep; LOR decreased WMINS and SWS, increased REM sleep, compared to PLC; sleep returned to normal when switched to PLC
Wolf *et al.*, 2001	150 mg	Fluoxetine 20 mg	Depressed geriatric patients	19	6 weeks	TRIM sig higher SE ($p < 0.05$), longer TST ($p < 0.05$), shorter WASO ($p < 0.01$); FLX decreased REM% ($p < 0.01$) increased REML ($p < 0.05$)
Sonntag *et al.*, 1996	See imipramine					
Ware *et al.*, 1989	See imipramine					

Desipramine						
Kupfer *et al.*, 1991	100–200 mg	Fluvoxamine 200 mg	Depressed inpatients	35	4 weeks	DES sig reduced SL day 1, sig increased by day 7 to end ($p = 0.01$), sig increased stage 2 sleep day 1 to end ($p < 0.001$), sig reduced REM% at day 1, increased day 2 to end ($p < 0.001$), sig increased REML at day 1, decreased day 2 to end ($p < 0.001$); FLX sig increased SL at day 1 ($p < 0.001$), decreased day 7 to end (ns), sig increased WMINS at day 1 to end ($p < 0.001$), sig reduced SE at day 1, returning to baseline by day 7 ($p < 0.001$), sig reduced REM% by day 1, increasing at end ($p < 0.001$), sig increased REML by day 1, still further day 2, reduced from day 7 to end ($p < 0.001$); groups sig differed on SL (FLX > DES), SE (DES > FLX) and REML (FLX > DES)
Shipley *et al.*, 1985	1: 50 mg 2: 150 mg 3: 150–250 mg	Amitriptyline 50–150 mg	Depressed inpatients	33	4 weeks	Compared to baseline, DES 50 mg sig more WASO ($p < 0.01$), more stage 2 sleep ($p < 0.01$), less REM% ($p < 0.001$), greater REML ($p < 0.001$); DES 150 mg sig less REM%, greater REML (all $p < 0.001$); DES 150–250 mg sig more stage 1 sleep ($p < 0.05$), stage 2 sleep ($p < 0.01$), less REM% ($p < 0.001$), greater REML ($p < 0.001$); compared to AMI, DES sig more WASO ($p < 0.01$), more WMINS ($p < 0.01$), less TST ($p < 0.05$), poorer SE ($p < 0.01$) less REM time ($p < 0.01$)
Nortriptyline						
Hammack *et al.*, 2002	100 mg	Placebo	Patients with severe pain	51	9 weeks	TST increased by 0.5 h with NOR, decreased by 0.3 h with PLC ($p = 0.02$); NOR more likely to report sleepiness as a side effect than PLC (ns; $p = 0.09$)
Taylor, 1999	Mean 70.8 mg	Placebo	Elderly bereaved depressed patients	27	6 months	NOR decreased REM time and increased REM density; no change PLC; REM sleep NOR group reverted to baseline after withdrawal; subjective SQ returned to normal
Reynolds *et al.*, 1997	80–120 ng/mL	Placebo	Elderly recurrent depressed patients	40	1 year	NOR sig longer SL ($p = 0.02$), longer REML ($p = 0.01$), less REM proportion ($p = 0.001$) greater REMD ($p < 0.001$) more REM production throughout ($p < 0.001$)
Dothiepin						
Wilson *et al.*, 2002	75–150 mg	1: Fluoxetine 20 mg 2: Placebo	Healthy volunteers (male)	12	5 weeks	Both active drugs less REM sleep time than PLC day 10 ($p = 0.001$) and day 36 ($p = 0.04$); FLX group longer REML than PLC and DOT day 10 ($p = 0.003$); both active groups longer REML than PLC day 36 ($p = 0.03$); DOT group poorer SE than FLX and PLC day 36 ($p = 0.04$); FLX group more WMINS than DOT day 10 ($p = 0.03$)
Stephenson *et al.*, 2000	150 mg	Fluoxetine 20 mg	Depressed patients	125	6 weeks	No between-group differences on LSEQ scores, but disturbed sleep/drowsiness side effects reported more often in DOT group
Wilson *et al.*, 2000	See fluvoxamine					
Ramaekers *et al.*, 1995	75–150 mg	1: Fluoxetine 20 mg 2: Placebo	Healthy volunteers	18	22 days	DOT reported increased difficulty waking days 1–3 ($p = 0.043$), FLX on days 17–21 ($p = 0.02$); DOT days 1–3 estimated 43 min longer TST than PLC ($p = 0.02$)

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Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Ferguson *et al.*, 1994	150 mg/night	Doxepin 150 mg/night Placebo	Depressed patients	579	10 weeks	HAMDS sig reduced for DOT and DOX, compared to PLC ($p < 0.05$)
Corne and Hall, 1989	75–100 mg	Fluoxetine 40–60 mg	Depressed patients in primary care	100	6 weeks	No between-group differences on HAMDS, but tiredness/drowsiness side effects reported more often in DOT group and response quicker for DOT
Blacker *et al.*, 1988	See trazodone					
Doxepin						
Hajak *et al.*, 2001	25–50 mg	Placebo	Insomnia patients	47	4 weeks	DOX sig increased SE compared to PLC ($p < 0.05$); DOX sig improved SQ ($p < 0.001$); but, pts with severe insomnia rebound (after treatment withdrawal) were sig more likely to have taken DOX than PLC
Hajak *et al.*, 1996	25 mg	Placebo	Insomnia patients Healthy volunteers	10 5	3 weeks	DOX sig improved SL, TST, and WMINS in both study groups, compared to PLC
Ferguson *et al.*, 1994	See dothiepin					
Feighner *et al.*, 1986	100–225 mg	Bupropion 300–450 mg	Depressed patients	147	14 weeks	HAMDS sig improved in DOX, compared to BUP ($p < 0.05$)
Hameroff, 1984 Hameroff, 1982	Mean 200 mg	Placebo	Pain patients	60	6 weeks	Sig improvements in sleep for DOX, relative to PLC Same dataset as Hameroff, 1984
Lofepramine	No RCTs found					
Phenelzine	No RCTs found					
Tranylcypromine						
Nolen *et al.*, 1993	20–100 mg	Brofaromine 50–250 mg	Depressed patients	39	4 weeks	Both treatments sig increase REML ($p = 0.02$), more so BRO, slightly reduced stage 1 sleep (ns), sig increased stage 2 ($p < 0.001$), increased stage 3 (ns), and sig reduced stage 4 ($p = 0.001$); SWS reduced overall and approached sig ($p = 0.07$); both groups sig reduced REM ($p < 0.001$), particularly TRAN; shorter TST reports, more WASO and waking more tired with BRO, SL longer, but sleep deeper and more refreshed with TRAN ($p = 0.02$)
Isocarboxazid						
Giller *et al.*, 1982	20 mg	Placebo	Depressed outpatients	30	3 weeks	No HAMDS score changed overall, although those who responded best to active drug tended to report less sleep disturbance
Moclobemide						
Sogaard *et al.*, 1999	See sertraline					
Hannonen *et al.*, 1998	See amitriptyline					
Dingemanse *et al.*, 1992	450 mg	Toloxatone 200–400 mg	Healthy volunteers	12	8 days	No differences detected on sleep variables between groups
Ramaekers *et al.*, 1992	200 mg	1: Mianserin 10 mg 2: Placebo	Healthy volunteers	17	8 days	No differences in reports of SQ, but MIA group showed increased sleep, and reported daytime drowsiness/fatigue; MOC appeared to have little effect on sleep

Lemoine and Faivre, 1992	450 mg	Toloxatone 1000 mg	Depressed patients	268	4 weeks	Sig more MOC group showed improved sleep patterns than TOL
Citalopram						
Mendels *et al.*, 1999	20–80 mg	Placebo	Depressed patients, with melancholia	180	4 weeks	CIT group sig improvement in HAMDS relative to PLC ($p < 0.05$), but somnolence reported as side effect in twice as many CIT group as PLC
Leinonen *et al.*, 1999	See mirtazapine					
Rosenberg *et al.*, 1994	See imipramine					
Escitalopram	No RCTs found					
Sertraline						
Jindal *et al.*, 2003	Mean 142 mg	Placebo	Depressed patients	47	12 weeks	Compared to PLC, SER increased SWS 1st sleep cycle (ns), decreased SWS 2nd cycle ($p = 0.05$), longer REML ($p < 0.001$); SER group showed increase SL (ns), but no worsening SE; subjective (PQSI) ratings showed sig improvements for both groups ($p < 0.001$), but no between-groups differences
Paul *et al.*, 2002	50–150 mg	Placebo	Healthy volunteers	19	5 weeks	SER group showed more insomnia than PLC ($p = 0.002$), more nocturnal awakenings ($p = 0.007$) and more problems returning to sleep ($p > 0.001$)
Fava, 2002	50–200 mg	1: Fluoxetine 20–60 mg 2: Paroxetine 20–60 mg	Depressed patients	284	16 weeks	No between-group differences in respect of worsening or improvement of insomnia
Kroenke, 2001	Mean 72.8 mg	1: Paroxetine mean 23.5 mg 2: Fluoxetine mean 23.4 mg	Depressed patients (primary care)	573	9 months	All groups increase (improvement) MOS sleep scores, but no between-group differences
Lepine *et al.*, 2000	See clomipramine					
Sogaard *et al.*, 1999	50–100 mg	Moclobemide 300–450 mg	Atypical depressed patients	190	12 weeks	SER group showed sig improvement on LSEQ Item 4 (integrity of behaviour on waking); no other sleep differences between groups
Sechter, 1999	50–150 mg	Fluoxetine 20–6 mg	Depressed outpatients	238	24 weeks	SER near-sig improvement LSEQ scores relative to FLX at 18 weeks ($p = 0.08$; $p = 0.13$ at 24 weeks); sleep and rest item of SIP sig improvement in favour of SER ($p = 0.04$)
Moller *et al.*, 1998	See amitriptyline					
Bennie *et al.*, 1995	50–100 mg	Fluoxetine 20–40 mg	Depressed outpatients	286	6 weeks	Both groups showed sig improvement in LSEQ scores ($p < 0.05$), across all items; tendency for SER to present less difficulty in getting to sleep than FLX, while FLX tended to feel better on waking than SER, but no between-group differences overall
Aguglia *et al.*, 1993	Mean 72 mg	Fluoxetine mean 28 mg	Depressed outpatients	108	8 weeks	Both groups showed sig improvement in LSEQ scores, but there was no difference between the groups; although FLX group reported more insomnia than SER

Continues

Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Fluoxetine						
Winokur *et al.*, 2003	20–40 mg	Mirtazapine 15–45 mg	Depressed patients with insomnia	19	8 weeks	No between-group differences HAMDS; both sig reduction weeks 2–8 ($p < 0.05$); MIR better improvement SL and TST, compared to FLX; trend better improvement SE for MIR; FLX non-sig reduction SWS, increased WASO, increased REML, reduced REM time ($p = 0.033$), non-sig reduction SWS; MIR showed sig reduction SL ($p = 0.0015$), longer TST ($p = 0.04$), better SE ($p = 0.0004$), less WASO ($p = 0.0008$)
Dalery and Honig, 2003	20 mg	Fluvoxamine 100 mg	Depressed outpatients	184	6 weeks	Subjective sleep did not differ between groups until week 4, then SQ favoured FLUV (ns); HAMDS improvement was sig greater with FLUV than FLX at weeks 4 and 6
Wilson *et al.*, 2002	See dothiepin					
Fava, 2002	See sertraline					
Kroenke, 2001	See sertraline					
Stephenson *et al.*, 2000	See dothiepin					
Wolf *et al.*, 2001	See trimipramine					
Flament, 1999	See sertraline					
Sechter, 1999	See sertraline					
Wheatley, 1998	20–40 mg	Mirtazapine 15–60 mg	Depressed patients		6 weeks	No significant between-group differences
De Ronchi *et al.*, 1998	See amitriptyline					
Rush *et al.*, 1998	20–40 mg	Nefazodone 100–500 mg	Depressed outpatients	125	8 weeks	SE sig increased with NEF ($p = 0.05$), sig reduced with FLX ($p = 0.05$), FLX sig poorer than NEF ($p = 0.01$); WASO sig reduced with NEF ($p = 0.01$), sig increased with FLX ($p = 0.01$), FLX sig poorer than NEF ($p = 0.01$); SWS sig reduced both groups ($p = 0.01$); REM time sig reduced with FLX ($p = 0.01$), sig increased NEF ($p = 0.01$), NEF sig longer than FLX ($p = 0.01$); improvements sig greater for NEF than FLX on HAMDS (both improved) and sleep items on IDS-C and IDS-SR
Bennie *et al.*, 1995	See sertraline					
Gillin *et al.*, 1997	20 mg	Nefazodone 200–400 mg	Depressed patients	43	8 weeks	FLX sig decreased SE and REM time, increased WASO and REML; NEF sig decreased %AMT, but did not alter SE or WASO, REM time or REML; both groups showed sig improvement in some clinician- and patient-rated sleep disturbance scores, but NEF group generally improved more than FLX group
Armitage, 1997	20–40 mg	Nefazodone 200–500 mg	Depressed outpatients with insomnia	43	8 weeks	NEF increased SE, reduced WASO & %AMT; FLX increased WASO and REML, reduced REM time; NEF increased REM sleep, decreased REML; NEF greater SE, less WASO, less %AMT more REM sleep, shorter REML than FLX; sig greater improvement subjective sleep disturbance NEF than FLX; NEF reported better SQ
Satterlee and Faries, 1995	20 mg	Placebo	Depressed outpatients	89	8 weeks	HAMDS scores were improved for FLX relative to PLC (but ns); HAMDS scores worsened more often with PLC than FLX (ns); HAMDS scores improved more often with FLX than PLC (ns)

Nofzinger, 1995	See bupoprion					
Ramaekers *et al.*, 1995	See dothiepin					
Vasar *et al.*, 1994	20 mg	Placebo	Healthy volunteers	12	6 days	FLX sig increased SL ($p = 0.03$), reduced SE ($p = 0.03$), increased REML ($p = 0.04$), reduced REM% ($p = 0.01$), increased stage 2% ($p = 0.03$), increased stage 3% ($p = 0.02$), PLC ns; no within/between-group differences subjective sleep measures
Wolfe *et al.*, 1994	20 mg	Placebo	Fibromyalgia pts	42	6 weeks	SQ improved for FLX group ($p = 0.03$)
Kerr *et al.*, 1993	See amitriptyline					
Aguglia *et al.*, 1993	See sertraline					
Kerkhofs *et al.*, 1990	See amitriptyline					
Corne and Hall, 1989	See dothiepin					
Fluvoxamine						
Dalery and Honig, 2003	See fluoxetine					
Volkers *et al.*, 2002	See imipramine					
Silvestri *et al.*, 2001	100 mg	Paroxetine 20 mg	Healthy volunteers	14	1 month	PAR disrupted sleep more than FLUV; REM sleep suppressed (especially for FLUV) rebounded during withdrawal (especially for PAR)
Wilson *et al.*, 2000	100 mg	Dothiepin 100 mg	Healthy volunteers	12	3 days	FLUV shorter TST than DOT and PLC, more WMINS than PLC, poorer SE than DOT or PLC, more WASO than DOT or PLC, shorter SL than PLC, less time in REM sleep than PLC; DOT more SWS than PLC and FLUV, longer REML than OT or PLC; FLUV reported poorer SQ than DOT and PLC; DOT group reported more difficulty waking than FLUV and PLC, FLUV superior to PLC
Kupfer *et al.*, 1991	See desipramine					
Perez and Ashford, 1990	100–300 mg	Mianserin 60–180 mg	Depressed patients	63	6 weeks	LSEQ rating of SL sig better for MIA than FLUV at days 3 and 5 ($p < 0.05$), better rating of feelings on waking for FLUV than MIA at day 3 ($p < 0.05$); MIA better subjective SL, feeling more drowsy and fewer wakings than FLUV, FLUV easier waking up than MIA (all ns)
Paroxetine						
Ridout *et al.*, 2003	20 mg	1: Mirtazapine 15–30 mg (comparator; MIRC) 2: Mirtazapine 15 mg bid (positive control; MIRPC)	Healthy volunteers	12	10 days	PAR and MIR reported sig increased sedation (LARS); sig lengthening LSEQ SL PAR vs MIRC day 2, not PLC; sig reduction SL MIRPC vs PLC; SL sig higher PAR vs other treatments day 3; SL sig lower MIRPC vs other treatments week 4; LSEQ SQ sig poorer PAR vs PLC, sig better both MIR groups vs PLC; MESS indicated increased sleepiness with MIRPC days 1 and 2, with no other sig effects
Schatzberg *et al.*, 2002	20–40 mg	Mirtazapine 15–45 mg	Elderly depressed patients (65 +)	246	8 weeks	HAMDS score sig lower MIR than PAR weeks 1 ($p < 0.001$), 2 ($p = 0.006$) and 6 ($p = 0.005$); ns week 8 ($p = 0.062$)
Hicks *et al.*, 2002	20–40 mg	Nefazodone 400–600 mg	Depressed patients	40	8 weeks	TST, SE and WMINS worsened PAR, improved NEF, early in treatment, tended towards baseline by week 8; WASO sig worse by week 8 PAR; REML sig increased, REM time sig reduced PAR; NEF slightly decreased REML but increased REM time; subjective data (SMHSQ) indicated greater improvements in SQ and depth of sleep for NEF; no LSEQ factor showed sig between-group differences

Continues

Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Capaci and Hepguler, 2002	See amitriptyline					
Fava, 2002	See sertraline					
Kroenke, 2001	See sertraline					
Silvestri *et al.*, 2001	See fluvoxamine					
Ruwe, 2001	40 mg	1: Mirtazapine 30 mg 2: Combination MIR/PAR (CT)	Healthy volunteers	24	6 days	LSEQ: CT got to sleep more easily and quickly, felt more drowsy at sleep onset than PAR alone; CT group felt less drowsy at sleep onset than MIR alone; no between-group differences SQ; CT tended to have greater difficulty waking than PAR alone; no different to MIR alone; CT felt more tired on waking, PAR alone; no different to MIR alone
Kiev, 1997	See fluvoxamine					
Sharpley *et al.*, 1996	30 mg	Nefazodone 400 mg	Healthy volunteers	37	17 days	PAR reduced REM sleep, increased REML and WASO, reduced TST and SE; NEF did not alter REM sleep and had little effect on sleep continuity
Staner *et al.*, 1995	See amitriptyline					
Robbe and Hanlon, 1995	1: 20 mg 2: 40 mg	1: Amitriptyline 75 mg 2: Placebo	Healthy volunteers	16	8 days	AMI group showed severe drowsiness, but this disappeared after 1 week; PAR 20 mg had no effect on sleep; PAR 40 mg group showed poorer SQ
Wade and Aitken, 1993	15–30 mg	am vs pm dosing	Depressed patients	91	6 weeks	HAMDS sig better for a.m. dosing; trend towards better LSEQ scores for a.m. dosing
Dunbar *et al.*, 1993	10–50 mg	Placebo	Depressed patients	336	6 weeks	HAMDS scores sig more reduced for PAR than PLC at each week of trial ($p < 0.05$)
Dorman, 1992	15 mg	Mianserin 30 mg	Elderly depressed	60	6 weeks	6 of 10 LSEQ scores sig improved PAR, 1 factor sig increased MIA ($p < 0.05$); 4 factors worsened MIA, mostly re poorer waking (ns)
Claghorn, 1992a	10–50 mg	Placebo	Depressed patients	336	6 weeks	Same dataset as Dunbar, 1993
Claghorn, 1992b	10–50 mg	Placebo	Depressed patients	336	6 weeks	Same dataset as Dunbar, 1993
Kiev, 1992	20 mg	Placebo	Depressed patients	81	6 weeks	Sig greater decrease in HAMDS for PAR (−2.41) than PLC (−0.81; $p = 0.001$)
Maprotiline						
Edwards, 1983	See mianserin					
Venlafaxine						
Guelfi *et al.*, 2001	75–375 mg	Mirtazapine 15–60 mg	Depressed patients	157	8 weeks	MIR sig better HAMDS than VEN at all time points ($p = 0.03$)
Luthringer *et al.*, 1996	Up to 225 mg	Placebo	Depressed inpatients	24	1 month	VEN sig less REM time than PLC week 1 and month 1,VEN sig reduced REM week 1 ($p < 0.05$); REML sig longer VEN than PLC at both time points, VEN sig increase REML week 1 ($p < 0.01$); VEN more WASO than PLC, sig so month 1 ($p < 0.05$)
Cunningham *et al.*, 1994	25–200 mg	1: Trazodone 50–500 mg 2: Placebo	Depressed patients	225	6 weeks	HAMDS scores reduced for all groups by week 6; TRZ sig more than VEN and PLC; VEN HAMDS remained higher PLC

Reboxetine	No RCTs found					
Trazodone						
Le Bon *et al.*, 2003	100 mg	Placebo	Alcohol dependent patients	16	4 weeks	TRZ increased SE immediately through to 4 weeks; no improvement for PLC; TRZ also improved WASO, %AMT, and non-REM sleep
Saletu-Zyhlarz *et al.*, 2001	100 mg	Placebo	Insomnia patients with dysthymia	11	3 nights	TRZ associated with sig increase in SWS, increase in REML and decrease in REM% ($p < 0.05$)
Mashiko *et al.*, 1999	50, 75, 100 mg	Dose ranging	Depressed patients with insomnia	75	4 weeks	TRZ 50 mg and 75 mg sig better improvement HAMDS and HAMAS; 50 mg sig better than 100 mg; self-rated TST sig longer for 50 mg vs 100 mg, and 75 mg vs 100 mg
Walsh *et al.*, 1998	50 mg	1: Zolpidem 10 mg 2: Placebo	Primary insomniac patients	306	2 weeks	Both groups sig better ratings ease falling asleep ($p = 0.005$), WASO ($p = 0.04$), WMINS ($p = 0.002$) and SQ ($p = 0.003$) than PLC, no differences TRZ vs ZOL; SL decreased and TST increased ZOL and TRZ ($p < 0.05$), SL sig shorter ZOL than TRZ ($p = 0.037$)
Ware *et al.*, 1994	100 mg	1: Nefazodone 200 mg 2: Buspirone 10 mg 3: Placebo	Healthy volunteers	12	3 nights	TRZ sig fewer WASO than PLC; NEF sig less % stage 2 sleep than all other groups, sig less stage 3% than TRZ and BUS; NEF sig more REM% than PLC, but TRZ and BUS sig less REM% than PLC; TRZ and BUS sig longer REML than NEF and than PLC (all sig *post-hoc* comparisons to $p = 0.05$)
Weisler, 1994	150–400 mg	Bupropion 225–450 mg	Depressed patients	124	6 weeks	HAMDS scores sig improved for TRZ at days 7 ($p < 0.001$) and 14 ($p < 0.05$)
Nierenberg, 1994	50–100 mg	Placebo	Depressed patients, with insomnia	17	11 days	TRZ sig lower (better) PSQI TST score ($p = 0.003$), sig lower overall score ($p = 0.01$) than PLC, TRZ near sig lower scores than PLC on SQ and SL ($p = 0.06$); Y-NH HDSI sleep scores sig better for TRZ than PLC middle insomnia ($p = 0.03$), late insomnia ($p = 0.005$) and overall sleep scores ($p = 0.008$); more pts improved with TRZ than PLC on PQSI ($p = 0.004$) and Y-NH HDSI sleep scores ($p = 0.008$)
Cunningham *et al.*, 1994	See venlafaxine					
Moon and Davey, 1988	150 mg (night)	Mianserin 30–60 mg (night)	Depressed patients	39	6 weeks	Both groups showed sig improvements on LSEQ factors for ease of getting to sleep, sleep quality, ease of waking, and feelings upon waking ($p < 0.0001$), but no sig differences between them; TRZ improved at faster rate than MIA
Blacker *et al.*, 1988	150 mg	Amitriptyline 75–100 mg Dothiepin 75–150 mg Mianserin 30–75 mg	Depressed patients	227	6 weeks	All groups showed improved ease of getting to sleep and quality of sleep; this was immediate, although greatest for TRZ and DOT (p values not specified); feelings upon awakening were impaired in all groups until day 7, when these measures improved (in all groups except MIA, where improvement started at day 14)
Nefazodone						
Hicks *et al.*, 2002	See paroxetine					
Rush *et al.*, 1998	See fluoxetine					
Feighner *et al.*, 1998	100–600 mg	Placebo	Depressed patients	120	6 weeks	HAMDS scores sig better improved with NEF (−2.3) than PLC (−1.1; $p < 0.01$)

Continues

Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Vogel *et al.*, 1998	200–400 mg	Placebo	Healthy volunteers	22	16 days	REM time, REML, REMD and REM% all remained unchanged, relative to baseline and PLC; TST sig less NEF than PLC day 1 ($p < 0.05$), normalised by day 2; WMINS sig more with NEF than PLC day 1 ($p < 0.05$)
Gillin, 1997	See fluoxetine					
Armitage, 1997	See fluoxetine					
Sharpley *et al.*, 1996	See paroxetine					
Van Laar, 1995	See imipramine	1:Nefazodone 100 mg; 2: 200 mg; 3: Placebo	Healthy volunteers	24	1 week	SL sig greater for NEF 100 mg and NEF 200 mg, but not IMI, than PLC ($p < 0.05$) on day 1; no sig differences by day 7
Ware *et al.*, 1994	See trazodone					
Mianserin						
Ramaekers, 1998	15–60 mg	Mirtazapine 15–60 mg	Healthy volunteers	18	16 days	Subjective estimates TST increased MIR and MIA throughout ($p < 0.001$), no between-group differences; SQ rated better MIR than MIA ($p = 0.021$); drowsiness was reported sig more often with MIR and MIA, compared to PLC ($p = 0.015$)
Dorman, 1992	See paroxetine					
Ramaekers *et al.*, 1992	See moclobemide					
Perez and Ashford, 1990	See fluvoxamine					
Blacker *et al.*, 1988	See trazodone					
Moon and Davey, 1988	See trazodone					
Costa *et al.*, 1985	10–20 mg	Placebo	Depressed women	73	4 weeks	MIA reduced HAMDS, by end of trial; not PLC
Levin, 1985	30–60 mg	Nomifensine 75–150 mg and clobazam 22.5–45 mg	Depressed patients	40	3 weeks	MIA group showed sig greater reduction in HAMDS ($p < 0.05$) than co-therapy
Granier *et al.*, 1985	30 mg	Nomifensine 50 mg	Depressed patients	61	4 weeks	MIA greater improvement in HAMDS scores than nomifensine ($p < 0.05$)
Van Moffaert, 1983	30 mg	Melitracen 30 mg and flupentixol 1.5 mg	Anxious depressed patients	90	4 weeks	MIA greater improvement in insomnia factor of HAMD than co-therapy, at weeks 1 ($p = 0.02$) and 4 ($p < 0.01$)
Edwards, 1983	30–90 mg	1: Maprotiline 75–225 mg 2: Placebo	Depressed outpatients	58	6 weeks	MIA sig better than PLC at reducing early insomnia day 14 ($p < 0.05$), no other sig between-group differences HAMDS; no sig between-group differences LSEQ, but all sig reduced throughout (including PLC)
Smith and Naylor, 1978	30 mg	Placebo	Manic-depressive psychosis depressed	39	2 weeks	MIA group sig improvements nurse-observed TST, compared to PLC, weeks 1 ($p < 0.005$) and 2 ($p < 0.05$); patient-rated estimates of TST sig improved MIA vs PLC weeks 1 ($p = 0.02$) and 2 ($p < 0.01$); self-rated SL shorter MIA than PLC week 1 ($p < 0.01$); pts woke sig later with MIA than PLC weeks 1 ($p < 0.01$) and 2 ($p < 0.05$)
Mirtazapine						
Winokur *et al.*, 2003	See fluoxetine					
Ridout *et al.*, 2003	See paroxetine					

Aslan *et al.*, 2002	30 mg	Placebo	Healthy young volunteers	20	3 nights	MIR improved sleep continuity, compared with PLC, increased SE, decreased WASO and WMINS; SWS time increased; no sig effect on REM sleep
Schatzberg *et al.*, 2002	See paroxetine					
Guelfi *et al.*, 2001	See venlafaxine					
Radhakishun, 2000	1: 30 mg 2: 15 mg week1, 30 mg week2	Dose ranging (fixed dose, FD vs escalating dose ED)	Depressed patients	140	2 weeks	LSEQ 'getting to sleep; GTS' improved both groups, similar between groups until week 2, when GTS for FD sig better than ED ($p = 0.021$); TST estimates increased both groups, but FD exceeded ED weeks 1 ($p = 0.01$) and 2 ($p = 0.04$); sig fewer FD pts than ED reported middle insomnia ($p = 0.042$) and early insomnia ($p = 0.008$) by week 2
Bruijn *et al.*, 1999	See imipramine					
Leinonen *et al.*, 1999	15–60 mg	Citalopram 20–60 mg	Depressed patients	270	8 weeks	MIR group showed faster 'improvement of sleep', SQ and improved alertness following awakening on LSEQ, relative to CIT
Wheatley, 1998	See fluoxetine					
Kasper, 1997	See amitriptyline					
Nomifensine						
Levin, 1985	See mianserin					
Granier *et al.*, 1985	See mianserin					
Fann, 1984	See imipramine					
Bupoprion						
Ott *et al.*, 2002	150–400 mg	Placebo	Depressed patients	20	1 week	No between-group differences, at 1 week relative to baseline; but BUP responders showed increase REML, non-responders showed decrease—a sig relationship
Haney *et al.*, 2001	300 mg	Placebo	Marijuana withdrawal patients	10	4 weeks	In withdrawal phase, problems with sleep were worse for BUP than PLC, particularly during first 6 days of withdrawal; SMHSQ 'difficulty sleeping' and TST were sig poorer with BUP between days 1–3 ($p < 0.005$) and days 4–6 ($p < 0.01$)
Shiffman *et al.*, 2000	1: 150 mg 2: 300 mg	Placebo	Non-depressed smokers	91	2 weeks	No differences found between BUP and PLC regarding HAMDS scores on nicotine withdrawal
Nofzinger, 1995	Mean 25 mg	1: Fluoxetine mean 428 mg 2: CBT	Depressed patients (male)	18	Up to 17 weeks	SE increased for all groups, but particularly for BUP ($p < 0.05$); REML increased with CBT, dramatically increased for FLX, but decreased for BUP ($p < 0.0001$), REM% was unchanged with CBT and FLX, but increased with BUP ($p < 0.01$)
Feighner *et al.*, 1986	See doxepin					
Fabre, 1983	300–600 mg	Placebo	Depressed inputs	75	4 weeks	Effects on sleep between the groups were limited

Continues

Table 1. Continued

Lead Author, Year	Study dose	Reference treatment	Subjects	*n*	Duration	Outcome, following treatment
Milnacipran						
Poirier *et al.*, 2004	50 mg	Placebo	Healthy volunteers	20	2 weeks	Subjective sleep ratings (adapted from LSEQ) improved but no between-group differences
Hindmarch, 2000	See amitriptyline					

Medication abbreviations: ALP Alprazolam ; AMI Amitriptyline; BRO Brofaromine; BUP Bupropion; BUS buspirone; CIT Citalopram; CLO Clomipramine; DES Desipramine; DOT Dothiepin; DOX Doxepin; FLUV Fluvoxamine; FLX Fluoxetine; IMI Imipramine; MIA Mianserin; MIL Milnacipran; MIR Mirtazapine; NEF Nefazodone; NOR Nortriptyline; PAR Paroxetine; PLC Placebo; SER Sertraline; TOL Toloxatone; TRAN Tranylcypromine; TRIM Trimipramine; TRZ Trazodone; VEN Venlafaxine; ZOL Zolpidem.
Other abbreviations: %AMT percentage of awake and movement time; CBT Cognitive behaviour therapy; EMA Early morning awakening; EMG Electromyogram (muscle activity); HAMAS Hamilton Rating Scale for Anxiety, Sleep Scores; HAMDS Hamilton Rating Scale for Depression, Sleep Scores; IDS-C Inventory for Depressive Symptomatology (Clinician-rated); IDS-SR (self rated); LARS Line Analogue Rating Scale for Sedation; LSEQ Leeds sleep evaluation questionnaire; MESS Milford Epworth sleepiness scale; MOS Medical Outcome Study scale; PQSI Pittsburgh Sleep Quality Index; PSG Polysomnography; REM Rapid Eye Movement Sleep; REMD REM density; REML REM Latency; REM% proportion time in REM sleep; SE Sleep efficiency; SIP Sickness Impact Profile; SL Sleep Latency; SMHSQ St Mary's Hospital Sleep Questionnaire; SQ Sleep Quality; SWS Slow Wave Sleep; TST Total Sleep Time; WASO Wakings After Sleep Onset; WMINS Length of those wakings; Y-NH HDSI Yale-New Haven Hospital Depression Symptom Inventory.

some of the more specific findings for each antidepressant are examined. Rather than duplicate the data from Table 1, only the most important aspects are described.

PHARMACOLOGICAL OVERVIEW

Several mechanisms are important in the effects of antidepressant treatment on sleep. Increases in the availability of serotonin and noradrenaline appear to be associated with the suppression of REM sleep, but also with increases in sleep fragmentation (Wilson and Argyropoulos, 2005). The pathways responsible for these actions vary across antidepressant class and with individual medications, but generally refer to action on pre-synaptic autoreceptors, post-synaptic 5HT receptor sites (such as the 5-HT_{1A} and 5-HT_2 receptors), α_1- and α_2-adrenoceptors and histamine H_1 receptors. 5-HT_{1A} stimulation may be associated with REM sleep suppression; 5-HT_2 agonism may be related to sleep disturbance. Inhibition of α_2-adrenoceptors increases availability of noradrenaline, and therefore may be associated with fragmentation of sleep. Blockade of the other receptor sites (α_1-adrenoceptors and histamine H_1) may facilitate sleep promotion (Wilson and Argyropoulos, 2005).

TRICYCLIC ANTIDEPRESSANTS (TCAs)

There is much variation between TCAs in the effect on sleep architecture, and with regard to sedating and alerting properties. The British Association for Psychopharmacology (BAP) guidelines (Anderson *et al.*, 2000) suggest that sedation is 'relatively common or strong' with amitriptyline, dothiepin and clomipramine, while this 'may occur or is moderately strong' with imipramine, desipramine and nortriptyline. Sedation may be useful in depressed patients with insomnia, but might not be welcome in those patients wishing to avoid daytime sleepiness.

The mechanisms thought to be responsible for sleep effects in TCAs vary with specific compounds. Most TCAs inhibit the reuptake of both serotonin and noradrenaline, but the relative extent that they do this varies, and may explain some of the differences in sedation and REM sleep suppression. All TCAs except lofepramine block histamine H_1 receptors, and all but desipramine block α_1-adrenoceptors. The blockade of histamine H_1 receptors may be related to sleep promotion (Haas and Panula, 2003), but the evidence for an effect on REM sleep or SWS is weak (Wilson and Argyropoulos, 2005). Antagonism of

α_1-adrenoceptors is more likely to explain the sedative properties of TCAs, as might the 5-HT_2 blockade action, as seen with amitriptyline and trimipramine (which are particularly associated with sedation).

AMITRIPTYLINE

Depressed patients

Staner *et al.* (1995) found that amitriptyline (150 mg) produced more alerting effects than paroxetine (30 mg). Kerkhofs *et al.* (1990) demonstrated that amitriptyline (150 mg) and fluoxetine (60 mg) both produced significant REM sleep suppression. Casper *et al.* (1994) showed that patients presented better improvement in early morning awakening, and nocturnal wakings with amitriptyline (100–150 mg) than imipramine (100–150 mg); although this was only for those who had responded to treatment. Kerr *et al.* (1993) observed that amitriptyline (75 mg) was associated with significantly shorter sleep latency, but more drowsiness, than fluoxetine (20 mg) on the Line Analogue Rating Scale for Sedation (LARS) scale. However, De Ronchi *et al.* (1998) found no between-group differences for patients in respect of Leeds Sleep Evaluation (LSEQ) scores between amitriptyline (50–100 mg) and fluoxetine (20 mg).

Other patient groups

Mertz *et al.* (1998) found that amitriptyline (50 mg) reduced REM sleep in gastroenterology patients, compared to placebo, while Carette *et al.* (1995) demonstrated fewer changes in REM sleep parameters in fibromyalgia patients (dosage, 25 mg). This is just one example where the dose may be a significant factor in contrasting findings. For fibromyalgia patients (Hannonen *et al.*, 1998), subjective sleep ratings were significantly improved from baseline with amitriptyline (25–37.5 mg), compared to placebo. In a study of cancer patients with neuropathic pain (Mercadante *et al.*, 2002), it was found that drowsiness was significantly higher with amitriptyline (25–30 mg) than placebo. In another study (Mertz *et al.*, 1998), amitriptyline (50 mg) was associated with poorer sleep efficiency for patients with functional dyspepsia, compared to placebo. In a study of patients with chronic pain (Versiani *et al.*, 1999), amitriptyline (50–250 mg) was associated with better improvements in Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) sleep scores than fluoxetine (20 mg), although daytime drowsiness was a significantly greater problem with amitriptyline.

Healthy participants

Rosenzweig *et al.* (1998) found that subject-rated alertness and behaviour upon waking was significantly poorer with amitriptyline (50 mg) than placebo. This hangover effect was confirmed by Hindmarch *et al.* (2000) who demonstrated that sedation and trouble waking were significantly worse for amitriptyline (50 mg), compared to placebo.

CLOMIPRAMINE

Clomipramine may be associated with sedation, but has also been linked with insomnia (Anderson *et al.*, 2000). While most TCAs suppress REM sleep to some extent, clomipramine appears to be the most marked in this respect (Winokur *et al.*, 2001). Clomipramine is associated with the most potent serotonin reuptake inhibition of all the TCAs (Wilson and Argyropoulos, 2005).

Depressed patients

Lepine *et al.* (2000) demonstrated no differences between clomipramine (50–150 mg) and sertraline (50–200 mg) on LSEQ and HAMD sleep scores, but both showed significant improvements on all four LSEQ factors (Ease of getting to sleep (EGS); perceived quality of sleep (QOS); ease of awakening (EOA) and behaviour following wakefulness (BFW)).

Healthy participants

Lacey *et al.* (1977) found that clomipramine (25–75 mg) was associated with slightly longer nocturnal awakenings than placebo, and almost completely suppressed REM sleep.

IMIPRAMINE

Depressed patients

Sonntag *et al.* (1996) demonstrated that imipramine (50–200 mg) significantly increased sleep latency, while trimipramine (50–250 mg) was associated with a non-significant decrease; imipramine was associated with significantly less total sleep time, and significantly more nocturnal awakenings than trimipramine. Volkers *et al.* (2002) found that imipramine (mean dose 220 mg) was associated with significantly more nocturnal restlessness than fluvoxamine (mean 201 mg).

Other patient groups

In a study of patients reporting panic disorder or agoraphobia, (Cassano *et al.*, 1994) imipramine (25–250 mg) was associated with more sedation than placebo (although less than alprazolam; 1–10 mg), but significantly more insomnia than placebo and alprazolam. Sonntag *et al.* (1996) found that imipramine (50–200 mg) was associated with decreased total sleep time, while this was increased with trimipramine (50–250 mg); sleep efficiency was significantly more improved with trimipramine but wakings were significantly more frequent with imipramine.

TRIMIPRAMINE

Depressed patients

Wolf *et al.* (2001) showed that trimipramine (150 mg) was associated with improved sleep efficiency, longer sleep and fewer nocturnal arousals, compared to fluoxetine (20 mg).

Other patient groups

Riemann *et al.* (2002) found that trimipramine (mean 100 mg) was not associated with REM sleep suppression, when compared to placebo with insomnia patients. Unlike other TCAs, which are associated with REM suppression, trimipramine is not associated with the reuptake inhibition of serotonin (Wilson and Argyropoulos, 2005).

DESIPRAMINE

Depressed patients

Kupfer *et al.* (1991) demonstrated that desipramine (100–200 mg) significantly reduced sleep latency after just one day of treatment, but this significantly increased again within a week and throughout the remainder of the 4-week study. Desipramine was associated with shorter sleep latency than fluvoxamine (200 mg), and presented better sleep efficiency. In another study (Shipley *et al.*, 1985), desipramine (50–250 mg) was associated with more nocturnal waking, shorter sleep and less efficient sleep than amitriptyline (50–150 mg). Unlike other TCAs, desipramine is not associated with α_1-adrenoceptor blockade (Wilson and Argyropoulos, 2005), which may explain why it does not promote sleep as well. It is also associated with less serotonin reuptake inhibition than most other TCAs.

NORTRIPTYLINE

Depressed patients

Reynolds, III *et al.* (1997) demonstrated that nortriptyline (80–120 mg) was associated with longer sleep latency than placebo. Nortriptyline also showed initial suppression of REM sleep, with prolonged REM latency and reduced REM proportion, but this rebounded in later REM periods to show greater REM production and density than placebo.

Other patient groups

In a study of patients with skin complaints (Hammack *et al.*, 2002), total sleep time improved for those treated with nortriptyline (100 mg), compared to placebo. However, daytime sleepiness was reported as a problem in the treatment group.

DOTHIEPIN

Depressed patients

Stephenson *et al.* (2000) demonstrated that drowsiness side effects were more common with dothiepin (150 mg) than fluoxetine (20 mg). Ferguson *et al.* (1994) found that HAMD sleep scores were significantly reduced with dothiepin (150 mg), compared to placebo (but were similar to doxepin). Blacker *et al.* (1988) showed that dothiepin (75–150 mg) was associated with more immediate improvement of EGS and QOS perceptions on LSEQ than amitriptyline (75–100 mg) or mianserin (30–75 mg), although it was similar to trazodone (150 mg). LSEQ perceptions of BFW were poor during the first week for all the comparator compounds, but improved thereafter.

Healthy participants

Ramaekers *et al.* (1995) found that dothiepin (75–150 mg) was associated with increased trouble in waking, but longer total sleep time than placebo. Wilson *et al.* (2002) demonstrated that dothiepin (75–150 mg) was associated with poorer sleep efficiency than placebo (and fluoxetine 20 mg), but shorter nocturnal awakenings than fluoxetine; REM sleep latency was significantly shorter for dothiepin than for fluoxetine. Wilson *et al.* (2000) showed that dothiepin (100 mg) was associated with longer TST, shorter nocturnal disturbances, better sleep efficiency and better sleep quality than fluvoxamine (100 mg).

DOXEPIN

Depressed patients

Ferguson *et al.* (1994) found that clinician-rated HAMD sleep scores were significantly reduced with doxepin (150 mg), compared to placebo, while Feighner *et al.* (1986) showed that doxepin (100–225 mg) was related to significantly better improvements on these scores than bupropion (300–450 mg).

Other patient groups

Sleep efficiency and sleep quality were significantly improved for insomnia patients taking doxepin (25–50 mg), compared to placebo (Hajak *et al.*, 2001), while doxepin (25 mg) was associated with significantly increased total sleep time, and significantly reduced sleep latency and length of nocturnal awakenings, compared to placebo with insomnia patients and healthy volunteers (Hajak *et al.*, 1996).

MONOAMINE OXIDASE INHIBITORS (MAOIs)

MAOIs have been associated with increased sleep latency, poorer sleep efficiency and increased nocturnal disturbances (Winokur *et al.*, 2001). Insomnia has been reported for phenelzine, tranylcypromine and isocarboxazid (Anderson *et al.*, 2000), while significant REM sleep suppression has been noted with phenelzine and tranylcypromine (Winokur *et al.*, 2001). However, REM rebound is noted subsequent to the withdrawal of medication (Kupfer and Bowers Jr, 1972). There is a paucity of RCTs with MAOIs. Moclobemide, a reversible MAOI, has been associated with less REM sleep suppression than traditional MAOIs (Winokur *et al.*, 2001). Sedation is not reported with moclobemide, although minor insomnia has been noted (Anderson *et al.*, 2000). MAOIs increase the availability of monoamines, but REM suppression often appears later than with TCAs and SSRIs (Wyatt *et al.*, 1971).

TRANYLCYPROMINE

Depressed patients

Nolen *et al.* (1993) found that tranylcypromine (20–100 mg) significantly increased REM sleep latency and almost completely suppressed REM sleep overall. Sleep latency was also increased, but patients reported deeper and more refreshed sleep than with brofaromine (50–250 mg).

ISOCARBOXAZID

Depressed patients

Giller *et al.* (1982) demonstrated that isocarboxazid (20 mg) did not differ from placebo on HAMD sleep scores, but treatment responders tended to sleep better overall with isocarboxazid than with placebo.

MOCLOBEMIDE

Depressed patients

Sogaard *et al.* (1999) found that moclobemide (300–450 mg) was associated with poorer BFW scores on LSEQ than sertraline, while sleep was observed to better with moclobemide (450 mg) than with toloxatone (100 mg; (Lemoine and Mirabaud, 1992)).

Other patient groups

Hannonen *et al.* (1998) demonstrated that moclobemide (450–600 mg) was associated with poorer subjective sleep satisfaction and fatigue (not assessed with a specific scale) than amitriptyline (25–37.5 mg) in patients with fibromyalgia.

Healthy participants

Two trials involving moclobemide with healthy participants ((Dingemanse *et al.*, 1992), 450 mg; (Ramaekers *et al.*, 1992), 200 mg) suggest that moclobemide has no effect on sleep, when compared to placebo or other antidepressants.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

SSRIs are frequently associated with insomnia (Anderson *et al.*, 2000); around one-quarter of depressed patients in clinical trials report insomnia (Winokur *et al.*, 2001). Less well documented is that SSRIs may cause daytime somnolence, particularly at higher doses (Beasley Jr *et al.*, 1992). EEG studies of sleep confirm that SSRIs immediately suppress REM sleep, and continue to do so throughout treatment; REM parameters return to normal once the SSRI is discontinued (Winokur *et al.*, 2001).

The observed effects on sleep of SSRIs are thought to be due to the effects of increased levels of on 5-HT_{1A} and 5-HT_2 receptors. Activation of 5-HT_{1A} receptors is probably responsible for REM suppression (Gillin *et al.*, 1994), but is unlikely to mediate sleep fragmentation. This is more likely to be due to

stimulation of 5-HT_2 receptors (Lawlor *et al.*, 1991). By definition, SSRIs block serotonin reuptake, but some also block noradrenaline reuptake. Both actions have been associated with REM suppression and sleep disruption (Wilson and Argyropoulos, 2005).

CITALOPRAM

Depressed patients

Mendels *et al.* (1999) found that citalopram (20–80 mg) was associated with significant improvements in HAMD sleep scores, relative to placebo; although daytime sleepiness was a significantly greater problem for those taking citalopram than for placebo. Rosenberg *et al.* (1994) demonstrated that citalopram (10–60 mg) was associated with significantly better HAMD sleep scores (from baseline), but did not differ from imipramine (50–100 mg). Leinonen *et al.* (1999) showed that subjective ratings for all LSEQ factors significantly improved with citalopram (20–60 mg), although not as quickly as with mirtazapine (15–60 mg).

ESCITALOPRAM

Escitalopram is a relatively new antidepressant in the SSRI class. It has been developed from one of the isomers of citalopram, so whilst chemically identical, it may be more beneficial than citalopram if the efficacy elements reside in that single isomer; it may also possess less side effects than the original combination. There are currently no RCTs that specifically examine escitalopram in placebo or comparator trials. In a recent pooled analysis (Lader *et al.*, 2005), which compares data from RCTs involving citalopram and escitalopram, it was shown that escitalopram (10–20 mg) showed significantly better improvements on the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) item 4 (sleep) at all time points (weeks 1, 4, 6 and 8); citalopram (20–40 mg) was only significantly better at week 6. The proportion of patients with sleep problems (at baseline MADRS item $4 \geq 4$) improving by endpoint (MADRS item $4 \leq 1$) was significantly higher with escitalopram than citalopram. However, prospective RCTs specifically examining sleep are required.

SERTRALINE

Depressed patients

Jindal *et al.* (2003) found that sertraline (mean 142 mg) suppressed REM sleep and increased sleep latency (although not significantly), compared to placebo. Lepine *et al.* (2000) showed that sertraline (50–200 mg) and clomipramine (50–150 mg) significantly improved LSEQ (all factors) and HAMD sleep scores, but there were no between-group differences. Bennie *et al.* (1995) demonstrated that sertraline (50–100 mg) was associated with fewer reports of trouble in sleep initiation than fluoxetine (20–40 mg), but with poorer perceptions on waking. Although overall LSEQ scores were significantly improved for both groups, they differed on individual items: sertraline showed better EGS scores than fluoxetine, but poorer EOA and BFW.

Healthy participants

Paul *et al.* (2002) found that sertraline (50–150 mg) was associated with significantly more insomnia than with placebo.

FLUOXETINE

Depressed patients

Rush *et al.* (1998) found that sleep was significantly less efficient, and nocturnal awakenings were significantly greater, with fluoxetine (20–40 mg) when compared to nefazodone (100–500 mg). Fluoxetine significantly suppressed REM sleep, while nefazodone significantly increased the time spent in REM sleep. Wolf *et al.* (2001) demonstrated that fluoxetine (20 mg) was associated with less efficient, shorter and more disrupted sleep than trimipramine (150 mg); fluoxetine suppressed REM sleep, whereas trimipramine did not. Satterlee and Faries (1995) showed that HAMD sleep scores tended to show better improvement for fluoxetine (20 mg) than placebo, but this was not significant. Winokur *et al.* (2003) found no differences between fluoxetine (20–40 mg) and mirtazapine (15–45 mg) in respect of HAMD sleep scores; both showing significant improvements. However, improvements in sleep latency and total sleep time were not as marked for fluoxetine as they were for mirtazapine, which resulted in more efficient sleep and less nocturnal disturbances than fluoxetine.

Other patient groups

Wolfe *et al.* (1994) found that self-reported sleep quality perceptions were significantly better with fluoxetine (20 mg) than placebo for patients with fibromyalgia.

Healthy participants

Vasar *et al.* (1994) demonstrated that fluoxetine (20 mg) increased REM sleep latency and reduced overall REM proportion, increased sleep stages 2 and 3, increased sleep latency and worsened sleep efficiency, compared to placebo.

FLUVOXAMINE

Depressed patients

Volkers *et al.* (2002) found that fluvoxamine (mean 201 mg) was associated with more fragmented sleep than imipramine (mean 220 mg), while (Kupfer *et al.*, 1991) demonstrated greater sleep disruption for fluvoxamine (200 mg) than desipramine (100–200 mg). Perez and Ashford (1990) showed that fluvoxamine (100–300 mg) was associated with poorer EGS ratings on the LSEQ than mianserin (60–180 mg) but fluvoxamine was related to better BFW ratings. While fluvoxamine (100 mg) and fluoxetine (20 mg) did not differ in their effect on sleep in the first month of treatment, after that HAMD sleep scores were significantly better for fluvoxamine (Dalery and Honig, 2003).

Healthy participants

Silvestri *et al.* (2001) found that fluvoxamine (100 mg) was less disruptive to sleep than paroxetine (20 mg), but tended to be associated with greater REM sleep suppression. Wilson *et al.* (2000) demonstrated that fluvoxamine (100 mg) was associated with shorter and more disrupted sleep than with dothiepin (100 mg) or placebo. Although poorer subjective sleep quality was reported for fluvoxamine than dothiepin, perceptions upon waking were better.

PAROXETINE

Depressed patients

Dunbar *et al.* (1993) found that HAMD sleep scores were significantly more improved with paroxetine (10–50 mg) than placebo. Staner *et al.* (1995) showed that paroxetine (30 mg) was more alerting than amitriptyline (150 mg). Sleep quality was rated significantly more poorly with higher doses of paroxetine (40 mg vs 20 mg) than with amitriptyline (75 mg) or placebo (Robbe and O'Hanlon, 1995). Schatzberg *et al.* (2002) demonstrated that HAMD sleep scores were poorer with paroxetine (20–40 mg) than mirtazapine (15–45 mg). Hicks *et al.* (2002) found that sleep time was less, and disruption greater, for paroxetine (20–40 mg) compared to nefazodone (400–600 mg). REM sleep was shown to be significantly more suppressed with paroxetine than nefazodone, and subjective sleep ratings showed greater improvements with nefazodone. Dorman (1992) demonstrated that LSEQ scores were significantly more likely to be improved with paroxetine (15 mg) than mianserin (30 mg); paroxetine was significantly improved from baseline on all four factors; mianserin only for BFW. In an RCT where the time of dose was randomised (Wade and Aitken, 1993), HAMD scores were significantly better for morning doses of paroxetine (15–30 mg) than evening doses.

Other patient groups

Capaci and Hepguler (2002) found that sleep disruption did not improve as well with paroxetine (20–40 mg) as it did for amitriptyline (10–20 mg) in fibromyalgia patients.

Healthy participants

Ridout *et al.* (2003) demonstrated that paroxetine (20 mg) was associated with longer sleep latency and poorer reports of sleep quality than mirtazapine (15–30 mg). Sharpley *et al.* (1996) observed greater suppression of REM sleep for paroxetine (30 mg) than for nefazodone (400 mg).

OTHER ANTIDEPRESSANTS

Venlafaxine

Venlafaxine blocks the reuptake of serotonin and noradrenaline, mostly the former in lower doses (less than 150 mg), with little effect on post-synaptic receptor sites. Increases in these monoamines are related to REM suppression and sleep fragmentation (Wilson and Argyropoulos, 2005).

Depressed patients. Luthringer *et al.* (1996) found that venlafaxine (225 mg) was associated with significant REM sleep reduction, and significantly increased nocturnal disturbance, compared to placebo. Cunningham *et al.* (1994) demonstrated that HAMD sleep scores were improved following venlafaxine (25–200 mg), but significantly less so than with trazodone, and no different to placebo. Guelfi *et al.* (2001) showed that HAMD sleep scores were also significantly poorer for venlafaxine (75–375 mg) than mirtazapine (15–60 mg).

Reboxetine

Reboxetine inhibits the reuptake of noradrenaline, and is not associated with direct activity at post-synaptic receptor sites. No RCTs were found in the systematic review, but one uncontrolled study showed evidence of transient sleep disruption, but persistent REM suppression, with 2 mg (b.d.) of reboxetine in 12 dysthymic patients (Ferini-Strambi *et al.*, 2004), and (Kuenzel *et al.*, 2004) found nocturnal disturbance and reduced sleep efficiency with reboxetine (8–10 mg) in 8 depressed patients.

Trazodone

Trazodone is associated with weak serotonin reuptake blockade, and with antagonist actions at α_1-adrenoceptors, 5-HT_{1A} and 5-HT_2 receptors. The effects on α_1-adrenoceptor and 5-HT_2 receptor sites may explain why there is more evidence of sleep promotion with this compound. However, trazodone has also shown to suppress REM sleep in some studies (Mouret *et al.*, 1988), which seems at odds with the relative lack of serotonin reuptake antagonism and the inhibition of 5-HT_{1A} (Wilson and Argyropoulos, 2005). The reasons for this are unclear.

Depressed patients. Mashiko *et al.* (1999) found that sleep scores on HAMD were significantly better improved for trazodone (50–100 mg) than placebo, although the effect was better in lower doses. Nierenberg *et al.* (1994) demonstrated that trazodone (50–100 mg) was associated with significantly better patient-rated sleep quality (Pittsburgh Sleep Quality Index) and clinician-rated sleep scores (Yale-New Haven Hospital Depression Symptom Inventory) than was placebo. Blacker *et al.* (1988) observed better improvements in subjective sleep ratings with trazodone (150 mg) than with amitriptyline (75–100 mg) or mianserin (30–75 mg). Moon and Davey (1988) demonstrated similar improvements for all LSEQ scores with trazodone (150 mg) and mianserin (30–60 mg), although trazodone tended to show more rapid improvements.

Other patient groups

Le Bon *et al.* (2003) showed that trazodone (100 mg) was associated with significantly better sleep efficiency and significantly less nocturnal disturbance than placebo in alcohol dependent patients. Walsh *et al.* (1998) found that subjective ratings of sleep initiation, nocturnal awakenings and sleep quality were significantly better for trazodone (50 mg) than placebo for insomnia patients, but did not differ from the effects of the hypnotic drug zolpidem (10 mg). Saletu-Zyhlarz *et al.* (2001) observed significantly suppressed REM sleep for trazodone (100 mg), compared to placebo, in dysthymic insomnia patients.

Healthy participants

Ware *et al.* (1994) observed significantly more REM sleep suppression with trazodone (100 mg) than with nefazodone (200 mg).

NEFAZODONE

Nefazodone has mild serotonin reuptake blocking properties, and stronger 5-HT_2 antagonist effects. It is not associated with REM suppression, as might be expected (Wilson and Argyropoulos, 2005), The blockade of α_1-adrenoceptor sites, and the 5-HT_2 receptor probably underlie the beneficial effects on sleep continuity that have been observed.

Depressed patients

Feighner *et al.* (1998) found that nefazodone (100–600 mg) was associated with significantly better improvements in HAMD sleep scores than placebo. Previous analyses indicated that nefazodone was associated with less nocturnal disturbance than fluoxetine (Rush *et al.*, 1998) or paroxetine (Hicks *et al.*, 2002). While nefazodone shows clear benefits for sleep, it is no longer available in many countries.

Healthy participants

In contrast to some findings in depressed groups, Vogel *et al.* (1998) showed that nefazodone (200–400 mg) reduced total sleep time, and increased nocturnal awakenings, when compared to placebo in 120 healthy volunteers.

MIANSERIN

Mianserin is an antagonist at α_1-adrenoceptor sites and 5-HT_2 receptors, which may promote sleep but also with inhibition of the α_2-adrenoceptor, and with moderate inhibition of noradrenaline reuptake (Wilson and Argyropoulos, 2005), which may fragment sleep and suppress REM sleep. This compound has been associated with sleep promotion properties, particularly in comparison to SSRIs, as this review has shown, possibly through inhibition of histamine

H_1 receptors. There are no RCTs that explore the effects of mianserin on REM sleep, but uncontrolled studies have suggested slight suppression (Maeda *et al.*, 1991).

Depressed patients

Smith and Naylor (1978) found that mianserin (30 mg) was associated with significantly better nurse- and patient-rated improvements in total sleep time than placebo. Granier *et al.* (1985) demonstrated that mianserin (30 mg) was associated with significantly better improvements in HAMD sleep scores than nomifensine (50 mg). Mianserin (10–20 mg) was associated with significantly reduced HAMD sleep scores compared to placebo for depressed women with cancer (Costa *et al.*, 1985). However, this may have been compounded by the addition of the hypnotic drug nitrazepam (2.5–10 mg) for those patients with persistent insomnia.

Mirtazapine

Mirtazapine blocks α_2-autorecptors, 5-HT_2 receptors and H_1 receptors. α_2-adrenoceptor inhibition increases noradrenaline, thus suppressing REM sleep and disrupting sleep continuity; while the other actions tend to promote sleep. The improvements in sleep with mirtazapine are more likely to be the result of 5-HT_2 receptor inhibition (Haddjeri *et al.*, 1995).

Depressed patients

Leinonen *et al.* (1999) found that mirtazapine (15–60 mg) was associated with more rapid improvements in QOS and BFW on the LSEQ than was citalopram (20–60 mg). Earlier analyses comparing mirtazapine to other antidepressants, indicated less nocturnal disturbance and better sleep efficiency than with fluoxetine (Winokur *et al.*, 2003) or paroxetine (Ridout *et al.*, 2003), and better HAMD sleep scores than with paroxetine (Schatzberg *et al.*, 2002) or venlafaxine (Guelfi *et al.*, 2001).

Healthy participants

Aslan *et al.* (2002) demonstrated that mirtazapine (30 mg) was associated with significantly greater improvements in sleep efficiency, including fewer nocturnal disturbances than with placebo, but did not affect REM sleep measures.

BUPROPION

Bupropion is used as an agent to facilitate smoking cessation, and as an antidepressant in the US and some other countries. Its mechanism of action is not fully understood, but may involve noradrenaline reuptake, which is associated with REM suppression, and enhanced dopamine availability (Wilson and Argyropoulos, 2005), which is not. However, RCT evidence suggests that bupoprion is associated with REM suppression.

Depressed patients

Ott *et al.* (2002) found no differences with regard to sleep measures between bupoprion (150–400 mg) and placebo, although treatment response was associated with significant REM suppression.

Other patient groups

Haney *et al.* (2001) observed that bupropion (300 mg) was associated with poorer sleep than placebo in patients withdrawing from marijuana; total sleep time and getting to sleep were particularly poor for those taking bupropion in the first 3 days of withdrawal. However, when nicotine smokers were examined during withdrawal, no differences were detected between bupropion (150–300 mg) and placebo (Shiffman *et al.*, 2000).

MILNACIPRAN

Milnacipran inhibits the reuptake of serotonin and noradrenaline (Bourin *et al.*, 2005), but does not blockade histamine H_1or the α_1-adrenoceptor site. It might be expected that this compound would be associated with REM suppression and less sedation, but RCTs are scarce. Uncontrolled studies suggest no long term effect on REM sleep, and improved sleep efficiency (Lemoine and Faivre, 2004).

Healthy participants

Poirier *et al.* (2004) demonstrated that milnacipran was associated with improvements in subjective sleep ratings (sleep latency, sleep quality and waking), but did not differ from placebo in this respect.

OTHER PSYCHOTROPIC MEDICATIONS

Since sleep disturbance is often found with antidepressants, particularly in the form of insomnia with

SSRIs, hypnotic medications have been added to an antidepressant to offset the sleep problem. The addition of the novel antipsychotic risperidone has been found to reduce sleep disturbance in resistant depression (Ostroff and Nelson, 1999), but there is much more evidence for hypnotics. In one study of SSRI-treated depressed patients (Asnis *et al.*, 1999), those receiving fluoxetine (≤ 40 mg), sertraline (≤ 100 mg) or paroxetine (≤ 40 mg), who reported significant insomnia, were entered into a double-blind phase where they were randomised to zolpidem (10 mg) or placebo for 4 weeks, followed by single-blind placebo for 1 week.

Those receiving zolpidem demonstrated improved sleep (longer TST, better sleep quality and reduced WASO) and significant improvements in subsequent daytime perceptions. In the single-blind phase of placebo, the zolpidem group presented significant worsening of sleep, but no evidence of withdrawal effects. In another study (Londborg *et al.*, 2000), depressed outpatients were randomised to fluoxetine (20 mg) plus clonazepam (0.5–1 mg), or fluoxetine plus placebo. Significantly more patients showed improvements in sleep disturbance in the co-therapy group than with placebo, although sedation was reported more often with co-therapy than with placebo.

SUMMARY

Antidepressants are associated with differing effects on sleep profiles, with variations between and within classes: sometimes there is a conflicting evidence for individual compounds. The effect on sleep is related to pharmacological properties such as the degree of inhibition of serotonin or noradrenaline reuptake, the effects on 5-HT_{1A} and 5-HT_2 receptor sites, and actions at α_1- and α_2-adrenoceptors, and histamine H_1 sites. The effect that an antidepressant has on sleep is important because it may influence the clinician's decision regarding which antidepressant to prescribe to which patient.

There is much variation in the reported effects on sleep from TCAs. Amitriptyline (Hindmarch *et al.*, 2000), trimipramine (Sonntag *et al.*, 1996), nortriptyline (Hammack *et al.*, 2002), dothiepin (Blacker *et al.*, 1988) and doxepin (Hajak *et al.*, 2001) have all been associated with sedation, while imipramine (Volkers *et al.*, 2002) and desipramine (Shipley *et al.*, 1985) are less likely to be linked with sedation, but have been associated with insomnia; the evidence is less clear with clomipramine. At the same time, amitriptyline (Rosenzweig *et al.*, 1998), nortriptyline (Hammack *et al.*, 2002) and (particularly) dothiepin (Wilson *et al.*, 2002) have frequently been linked with poorer reports of daytime drowsiness. Improved subjective ratings of sleep have been reported with amitriptyline (De Ronchi *et al.*, 1998), clomipramine (Lepine *et al.*, 2000), imipramine (Ware *et al.*, 1989) and doxepin (Hajak *et al.*, 2001).

Clinician ratings of sleep (via HAMDS) have improved with amitriptyline (Versiani *et al.*, 1999), clomipramine (Lepine *et al.*, 2000), imipramine (Rosenberg *et al.*, 1994), dothiepin (Corne and Hall, 1989) and doxepin (Feighner *et al.*, 1986). EEG studies suggest that sleep length and efficiency are increased, and nocturnal disturbances reduced, for amitriptyline (Casper *et al.*, 1994), clomipramine (Eberhard *et al.*, 1988), trimipramine (Wolf *et al.*, 2001), nortriptyline (Reynolds, III *et al.*, 1997) and doxepin (Hajak *et al.*, 1996); although one study of nortriptyline suggested longer sleep latency (Hammack *et al.*, 2002) and another found no improvement in total sleep time for amitriptyline (Raigrodski *et al.*, 2001). Greater disturbance, and less sleep, is reported with imipramine (Volkers *et al.*, 2002) and desipramine (Shipley *et al.*, 1985). REM sleep suppression is reported with all TCAs except trimipramine (Riemann *et al.*, 2002). Patients who report difficulty getting to sleep are more likely to benefit from amitriptyline, trimipramine, nortriptyline, dothiepin and doxepin. These patients are less likely to benefit from imipramine and desipramine.

Not much data is available on sleep effects with MAOIs. In general, they are associated with greater nocturnal disturbance and shorter sleep times, with insomnia common (Winokur *et al.*, 2001). MAOIs have been reported to significantly suppress REM sleep (Nolen *et al.*, 1993). The few RCTs that were found during this review appear to support these findings. Nevertheless, subjective reports of sleep were favourable with tranylcypromine (Nolen *et al.*, 1993) and isocarboxazid (Giller *et al.*, 1982). All the same, MAOIs appear to present few benefits for the troubled sleeper. The reversible MAOI moclobemide is less associated with REM sleep suppression, and appears not to affect sleep notably (Ramaekers *et al.*, 1992).

SSRIs are commonly associated with insomnia (Anderson *et al.*, 2000), although occasionally daytime sleepiness has been reported with higher doses (Beasley Jr *et al.*, 1992). Despite this, patients' subjective sleep reports whilst taking SSRIs are frequently positive, as are clinicians' ratings. However, EEG studies frequently show greater fragmentation of sleep with SSRIs. REM sleep suppression is frequently

found with these compounds. In RCTs, prolonged sleep latency and reduced sleep time have been noted with sertraline (Jindal *et al.*, 2003), fluoxetine (Gillin *et al.*, 1997), fluvoxamine (Wilson *et al.*, 2000) and paroxetine (Hicks *et al.*, 2002), particularly when compared to placebo and against the sedative TCAs. However, patient-rated LSEQ scores have been shown to improve with citalopram (Leinonen *et al.*, 1999), sertraline and fluoxetine (Aguglia *et al.*, 1993), comparing well with TCAs in this respect, although not so well as some of the newer antidepressants.

Clinician-rated HAMDS scores were improved in the trials that investigated citalopram (Mendels *et al.*, 1999), sertraline (Lepine *et al.*, 2000), fluoxetine (Winokur *et al.*, 2003), fluvoxamine (Dalery and Honig, 2003) and paroxetine (Dunbar *et al.*, 1993). It is unlikely that a patient with a history of sleep disturbance will benefit from SSRI treatment. There are few differences between SSRIs, unlike TCAs. Some studies suggest that sertraline and fluoxetine present similar improvements in LSEQ scores (Aguglia *et al.*, 1993), while others show better improvement with sertraline (Bennie *et al.*, 1995); sertraline was also shown to produce fewer reports of insomnia than fluoxetine. Fluvoxamine appears to be associated with less sleep disruption than paroxetine (Silvestri *et al.*, 2001).

No general comments can be made about 'other' antidepressants, since their mode of action varies widely. Venlafaxine and reboxetine appear to be similar to SSRIs in REM sleep suppression and nocturnal disturbance (Luthringer *et al.*, 1996), and to present similar improvements in clinician-rated HAMD sleep scores (Cunningham *et al.*, 1994). Trazodone has been found to have favourable sleep outcomes in a number of trials, showing better improvements in subjective sleep ratings than TCAs (Moon and Davey, 1988), and performing equally well against placebo with the hypnotic zolpidem in respect of insomnia and sleep time (Walsh *et al.*, 1998).

Nefazodone presents some of the more positive sleep outcomes of any antidepressant, frequently showing better sleep time and less disruption than SSRIs (Hicks *et al.*, 2002). Mianserin was shown to be associated with greater improvements in LSEQ ratings than SSRIs, but with poorer perceptions on waking (Perez and Ashford, 1990). Mirtazapine appears to compare well with TCAs on sleep time and nocturnal disturbance, with a quicker, but less sustained improvement profile (Bruijn *et al.*, 1999). HAMD sleep scores have been shown to be better with mirtazapine than venlafaxine (Guelfi *et al.*, 2001) and similar to fluoxetine (Winokur *et al.*, 2003).

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