Addiction

REVIEW

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Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis

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ABSTRACT

Aims To assess the effectiveness of current treatment approaches to assist benzodiazepine discontinuation. **Methods** A systematic review of approaches to benzodiazepine discontinuation in general practice and out-patient settings was undertaken. Routine care was compared with three treatment approaches: brief interventions, gradual dose reduction (GDR) and psychological interventions. GDR was compared with GDR plus psychological interventions or substitutive pharmacotherapies. **Results** Inclusion criteria were met by 24 studies, and a further eight were identified by future search. GDR [odds ratio (OR) = 5.96, confidence interval (CI) = 2.08–17.11] and brief interventions (OR = 4.37, CI = 2.28–8.40) provided superior cessation rates at post-treatment to routine care. Psychological treatment plus GDR were superior to both routine care (OR = 3.38, CI = 1.86–6.12) and GDR alone (OR = 1.82, CI = 1.25–2.67). However, substitutive pharmacotherapies did not add to the impact of GDR (OR = 1.30, CI = 0.97–1.73), and abrupt substitution of benzodiazepines by other pharmacotherapy was less effective than GDR alone (OR = 0.30, CI = 0.14–0.64). Few studies on any technique had significantly greater benzodiazepine discontinuation than controls at follow-up. **Conclusions** Providing an intervention is more effective than routine care. Psychological interventions may improve discontinuation above GDR alone. While some substitutive pharmacotherapies may have promise, current evidence is insufficient to support their use.

Keywords Benzodiazepines, intervention, meta-analysis, pharmacotherapy, review, withdrawal.

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INTRODUCTION

Despite widespread concern over the dependence produced by the sustained use of benzodiazepines, long-term prescription continues to be common [1]. In one study, 84% of 3234 benzodiazepine users identified in a study of 15 general practices were still using them 8 months later [2], and in the 1996 Australian National Health Survey [3], 58% of the 359 300 benzodiazepine users had been taking them for at least 6 months.

A qualitative study of benzodiazepine users identified that continued use of benzodiazepines was often related to feeling addicted within a short period of time of commencing, both because of adverse symptoms when they tried to stop them and because they had come to rely on them [4]. This finding supports earlier work that identified a range of symptoms that can occur when benzodiazepines are ceased [5]. Acknowledgement of the high risk of benzodiazepine dependence prompted the development of treatments to assist patients to reduce or cease benzodiazepine use. Strategies included general practitioners (GPs) sending letters to patients recommending that they reduce their use of benzodiazepines [6], gradual dose reduction (GDR) regimens [7], prescription of substitutive medication [8] and provision of psychological intervention in addition to GDR [9]. While these studies established the potential to engage patients in dose reduction regimens, ongoing prescription of benzodiazepines remains common, particularly when patients are elderly, benzodiazepine use is long-standing or prescriptions were initiated by another doctor [4].

A meta-analysis by Oude Voshaar *et al.* [10] reported that providing a targeted intervention was more effective than routine care, and that both substitutive

pharmacotherapy and psychological intervention provided an additive effect to GDR alone. Their review included both in-patient and out-patient settings. The degree of control over reductions in an in-patient setting means that in-patient studies offer little information on effective strategies for benzodiazepine reduction in situations where it is most commonly needed—general practices or out-patient clinics. A Cochrane collaboration review by Denis *et al.* [11] also examined substitutive pharmacotherapy, but very stringent inclusion criteria resulted in only eight studies being reviewed. A review is needed that focuses upon general practice or out-patient settings and adopts less restrictive criteria with greater clinical relevance, while retaining a focus on sound, randomized controlled trials (RCTs).

The current study aims to establish: (i) whether targeted intervention for benzodiazepine cessation in general practice or out-patient settings assists more patients to stop using them than routine care and (ii) whether adjunctive treatment is more effective than GDR alone. An assessment of the quality of the reviewed papers in relation to Consolidated Standards of Reporting Trials (CONSORT) criteria [12] is also reported.

METHOD

Identification of relevant publications

A systematic search of PsycLIT (1840–2005), MEDLINE (1966–2005) and EBASE (drugs and pharmacology) (1990–2005) was undertaken, to identify studies that evaluated the effectiveness of treatments for cessation of benzodiazepine use. Search terms (abuse or dependen* or addiction or overuse or misuse or chronic or long-term or cessation or withdraw* or reduc* or discontinu* or taper* or cutting) and (benzodiaz* or nitrazepam or temazepam or triazolam or flunitrazepam or midazolam or zopiclone or zolpidem or oxazepam or alprazolam or diazepam or lorazepam or clobazam or bromazepam or clonazepam or minor tranquil* or sedative* or hypnotic* or anxiolytic* or psychotropic*) and (random* or RCT) in the title, identified 278 papers. An additional 53 papers were identified from journal citations, and a future search conducted in 2007 found a further 16.

Inclusion criteria

The first and third authors undertook a two-phase process to determine the articles included in the meta-analysis. Both reviewed the studies independently and excluded any that were unrelated to benzodiazepine cessation, or were not RCTs. An agreement of 94% was achieved, with disagreements resolved by reviewing the full paper jointly (4%) or by adjudication by the second author (2%). Studies were included if they compared an adjunctive treatment with either routine care or GDR, and participants were out-patients who had used benzodiazepines continuously for 3 months or longer prior to the commencement of the study. Trials had at least 10 participants in each condition at baseline, and reported information had to allow calculation of cessation rates for each condition based on intention to treat. Agreement of 100% was achieved for the judgement that a study met inclusion criteria.

Quality of research studies

Based on the work of Moyer, Finney & Swearingen [13] and CONSORT criteria [12], a template and scoring system was developed to measure the methodological quality of studies included in the meta-analysis. The 18-item scale (described in Table 1) comprised four domains relating to: (i) patient sampling and description; (ii) treatment provision and specification; (iii) follow-up points and outcome; and (iv) research design. Each item was weighted to reflect its potential impact on treatment effects, giving total scores of 0–45. This total formed a methodological quality score (MQS) analogous to that developed by Miller & Wilbourne [14] for analysis of trials on treatment for alcohol problems. The current quality assessment represents an extension of criteria presented by Denis *et al.* [11], which were published subsequent to our adoption of the current criteria. Their assessment of quality included blinding, attrition bias, detection bias and presentation of an intention-to-treat analysis. The only criterion of Denis *et al.* [11] that we omitted was independence of allocations, which was a feature of few included studies. Denis *et al.* did not calculate an overall quality score.

Quality ratings were undertaken independently by the first three authors, with the first and second authors reviewing studies and their ratings subsequently to derive a consensus.

Statistical methods

Proportions of participants ceasing benzodiazepine use in each condition were the key outcome variables, as the goal of dose reduction is complete cessation. Intention-to-treat data were used to derive cessation rates at post-treatment and follow-up. The first post-treatment assessment was designated 'post-treatment' and second or subsequent assessments were regarded as 'follow-up/s'. Data were entered into the Cochrane Collaboration Review Manager software (RevMan version 4.2) [15], and fixed-effect Mantel–Haenszel odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for cessation rates at post-treatment and follow-up.

Table 1 Methodological quality scale.

Variable	*Score*	*Scoring criteria*	*No. of studies* *n = 32*	*(%)*
Patient sampling and description				
1. Number approached to participate	1	Overall	13	(40)
2. Number of initial participants	1	Overall	32	(100)
3. Dropouts over the study	1	Overall	3	(9)
	2	By condition	29	(91)
4. Follow-up rates (over 3 months)	2	70%+	1	(3)
	3	75%+	1	(3)
	4	80%+	2	(6)
	5	85%+	2	(6)
	6	90%+	18	(56)
5. Fulfilling formal BZ dependence criteria/degree of dependence symptoms	1	One or both overall	–	–
	2	One or both by condition	4	(13)
6. Initial BZ dose/duration of BZ use	1	One or both overall	5	(16)
	2	One or both by condition	25	(78)
7. Assessed presence of co-occurring disorders	1	Partial/overall data only	16	(50)
	2	Fully by condition	4	(13)
Treatment provision and specification				
8. Manuals/protocols used to guide treatment	1	Written instructions—overall treatment	17	(53)
	2	Written protocol—sessional aspects/time	6	(19)
	3	Fully manualized treatment of sessions	4	(13)
9. Treatment implementation/ adherence to protocol assessed	1	Any test of adherence (checklist by therapist)	2	(6)
	2	Independent assessment of treatment session content	2	(6)
	3	Detailed independent check, e.g. reviewing transcripts or tapes or direct observation	3	(9)
Follow-up points and outcome variables				
10. Maximum duration over which change is measured	1	= 3 months	7	(22)
	2	= 6 months	8	(25)
	3	= 12 months	9	(28)
11. Duration off BZ reported	1	Some indication, e.g. post- and follow-up or numbers participating	3	(9)
	2	Continuous assessment	9	(28)
12. Corroboration of self-reports (post-treatment)	1	Collateral	6	(19)
	2	Pill count	–	–
	3	Urine/blood screen	17	(53)
	4	Multiple	1	(3)
13. Corroboration of self-reports (follow-up)	1	Collateral	2	(6)
	2	Pill count	–	–
	3	Urine/blood screen	5	(16)
	4	Multiple	1	(3)
14. Number BZ free at post-treatment	1	Overall	–	–
	2	By condition	32	(100)
15. Number BZ free at follow-up	1	Overall	–	–
	2	By condition	17	(53)
Research design				
16. Additional treatment	1	Overall	–	–
	2	By condition	1	(3)
17. Data collectors not affiliated with treatment	2	Information provided	4	(13)
18. Data collectors unaware of patient treatment condition	2	Information provided	15	(47)

BZ: benzodiazepine.

RESULTS

Included studies

Initial scanning of 331 papers identified by the literature search resulted in 108 potentially relevant trials (Fig. 1), 24 of which met inclusion criteria. An additional eight trials were identified by future searches from these 24 studies.

Participant characteristics

Information on participants was highly variable across studies. No systematic associations were detected between outcomes and participants' age, gender or duration of use. Participant details are reported in Table 2.

Meta-analyses

Table 3 provides ORs and CIs for the included studies. The current meta-analyses either compared treatment with routine care or compared a more intensive with a less intensive treatment. Oude Voshaar *et al.* [16] compared routine care, GDR and GDR plus cognitive-behaviour therapy (CBT). The current paper split these data into three comparisons (routine versus GDR, and CBT versus both routine care and GDR). Two studies compared more than one substitutive pharmacotherapy with gradual data alone. In these cases, results for the substitutive pharmacotherapies were combined, to avoid double entry of the study in the analysis [17,18]. As Table 3 shows, the combination of medication conditions in those two

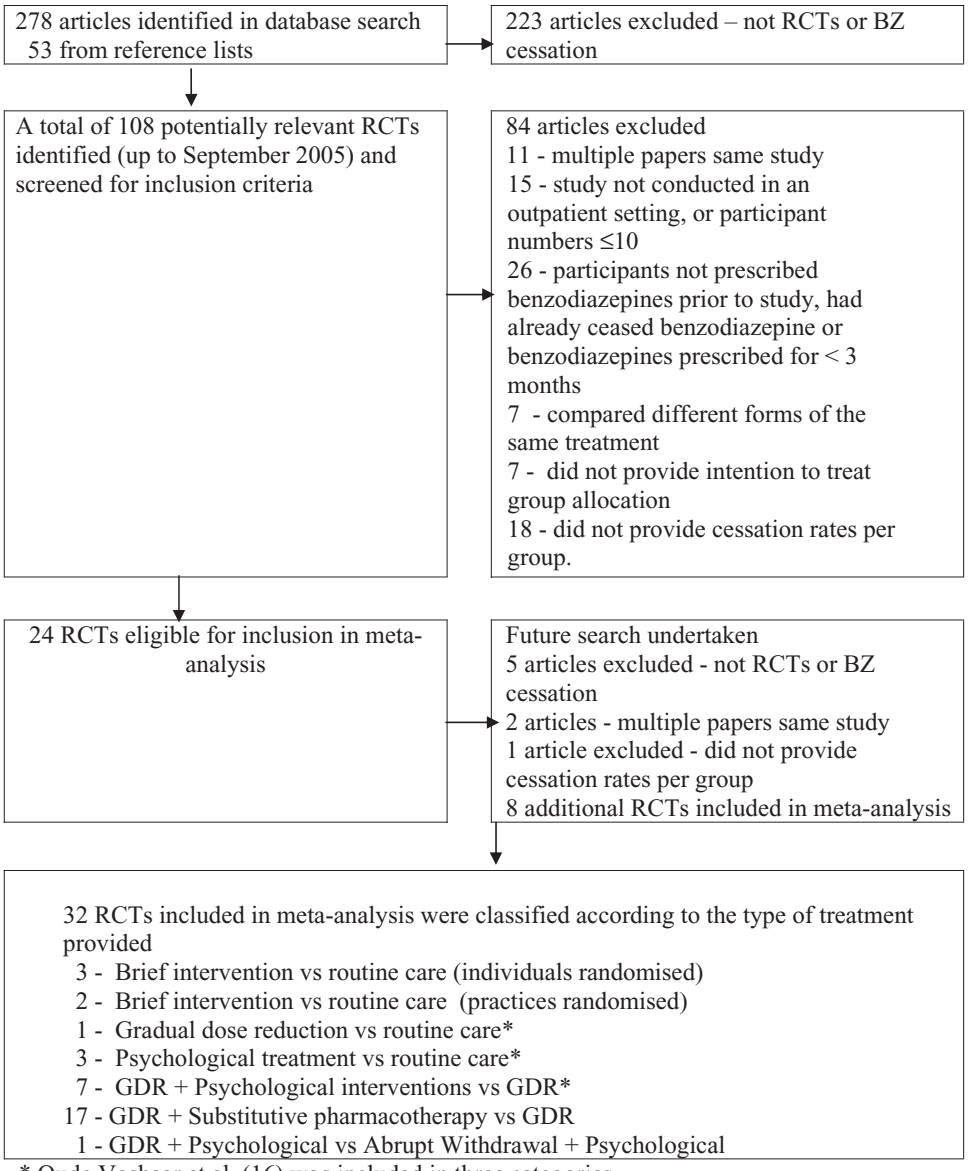

Figure 1 Progress through stages of the meta-analysis. BZ: benzodiazepine; GDR: gradual dose reduction; RCT: randomized controlled trial

Table 2 Participants, duration of withdrawal and treatment-setting.

Author	*Mean age*	*Women*	*Mean years of use*	*Withdrawal*	*Out-patient setting*
Comparison of treatment with routine care (RC)					
Brief intervention versus RC					
Individuals randomized					
Bashir *et al.* [19]	62	62%	14	–	GP
Heather *et al.* [20]	69	77%	13	–	GP
Vicens *et al.* [21]	–	–	–	–	GP
Practices randomized					
Gorgels *et al.* [22]	63	72%	–	–	GP
Niessen [23]	–	73%	–	–	GP
Gradual dose reduction (GDR) versus RC					
Oude Voshaar *et al.* [16]	63	71%	13	28	GP
Psychological interventions versus RC					
Giblin & Clift [24]	71	–	9	PC	
Jones [25]	–	79%		PC	GP
Oude Voshaar *et al.* [16]	63	69%	13	28	GP
GDR versus GDR plus additional treatment					
GDR plus psychological interventions (PI)					
Baillargeon *et al.* [26]	67	59%	13	56	OC
Gosselin *et al.* [27]	50	59%	7	84	GP
Morin *et al.* [28]	63	48%	19	70	OC
Otto *et al.* [29]	38	67%	–	49	OC
Oude Voshaar *et al.* [16]	63	71%	13	28	GP
Spiegel *et al.* [30]	38	81%	2	6.5[b]	OC
Vorma *et al.* [31]	40	45%	7	PC	AC
GDR plus gradual substitutive pharmacotherapy					
Ashton *et al.* [33]	42	61%	10	28	PsC
Di Costanzo & Rovea [34]	–	–	–	–	PsC
Garfinkel *et al.* [35]	69	74%	–	42	PsC
Hantouche [36]	44	72%	–	30	GP
Lader & Olajide [37]	39	58%	8	28	PsC
Lader *et al.* [38]	45	68%	–	–	PsC
Mercier-Guyon *et al.* [39]	41	–	–	14	GP
Morton & Lader [40]	46	67%	–	42	BC
Nakao *et al.* [41]	59	67%	11	56	OC
Rickels *et al.* [18]	47	51%	7[b]	42	PhC
Schweizer *et al.* [42]	47	52%	5	28	PhC
Tyrer *et al.* [43]	–	–	10[c]	56	OC
Udelman & Udelman [44]	42	52%	–	–	MC
Zitman & Couvee [45]	56	72%	6[b]	–	GP
GDR plus abrupt substitutive (AS) pharmacotherapy					
Cantopher *et al.* [46]	46	71%	10	70	PsC
Lemoine *et al.* [47]	48	69%	4[a]	28	PsC
Abrupt withdrawal (AW) plus AS pharmacotherapy					
Cialdella *et al.* [17]	54	58%	–	0	PhC
GDR plus PI versus AW plus PI					
Sanchez-Craig *et al.* [48]	41	50%	6[c]	PC	OC

GP: general practice; OC: out-patient clinic; PsC: psychiatric clinic; PhC: pharmacotherapy clinic; BC: benzodiazepine clinic; MC: multi-centre; AC: addiction clinic; PC: patient controlled. [a]Current episode; [b]average; [c]median.

trials did not affect outcomes substantially, as quit rates in those conditions were very similar.

Comparison of treatment with routine care

Three categories of comparisons between treatment and routine care were found, as follows.

Brief intervention versus routine care. Studies in this category involved a general practitioner (GP) sending a letter to patients who had received repeat prescriptions for 3 months or more, outlining the need to reduce benzodiazepine use. Some studies also mailed a booklet that provided advice on self-help strategies. Three studies that

Table 3 Study outcomes.

Author	Design/treatments	Intent to treat n	Post-treatment: Ceased use n	Post-treatment: Ceased use %	Post-treatment: OR (95% CI)	Follow-up: Ceased use n	Follow-up: Ceased use %	Follow-up: OR (95% CI)	Quality score MQS/45
Comparison of treatment with routine care									
Brief intervention (BI) versus routine care (RC)									
Individuals randomized									
Bashir *et al.* [19]	GP BI + self-help booklet	51	9	18%	3.93*				18
	No intervention	58	3	5%	(1.00–15.41)				
Heather *et al.* [20]	Offer of short consultation	98	10	10%	1.60				19
	GP letter	93	9	10%	(0.62–4.16)				
	RC + assessment	93	6	6%					
Vicens *et al.* [21]	BI	73	29	40%	21.09*	33	45%		19
	RC	66	2	3%	(4.78–92.97)	6	9%		
Practices randomized									
Gorgels *et al.* [22]	GP letter	2595	536	21%	2.33*				19
	RC	1821	183	10%	(1.95–2.79)				
Niessen [23]	GP letter	1395	107	8%	1.99*				24
	RC	7532	314	4%	(1.58–2.50)				
Gradual dose reduction (GDR) versus RC									
Oude Voshaar *et al.* [16]	GDR	73	37	51%	5.96*				
	RC	34	5	15%	(2.08–17.11)				
Psychological interventions (PI) versus RC									
Giblin & Clift [24]	GDR + PI	10	7	70%	21.00*	6	60%	13.5*	19
	RC	10	1	10%	(1.78–218.10)	1	10%	(1.20–152.21)	
Jones [25]	GDR + PI	112	21	19%	2.18*				18
	RC	115	11	10%	(1.00–4.77)				
Oude Voshaar *et al.* [16]	GDR + PI	73	33	45%	4.79*	33	45%	4.79*	23
	RC	34	5	15%	(1.67–13.74)	5	29%	(1.67–13.74)	
GDR plus additional treatment versus GDR									
GDR plus PI									
Baillargeon *et al.* [26]	GDR + PI	35	26	74%	4.99*	22	63%	3.38*	30
	GDR	30	11	37%	(1.73–14.42)	10	33%	(1.22–9.41)	
Gosselin *et al.* [27]	GDR + PI	31	23	74%	4.97*	20	65%	4.24*	24
	GDR + non-specific	30	11	37%	(1.66–14.84)	9	30%	(1.45–12.40)	
Morin *et al.* [28]	GDR + PI	27	23	85%	6.23*	16	59%	1.34	33
	GDR	25	12	48%	(1.66–23.32)	13	52%	(0.45–4.02)	
Otto *et al.* [29]	GDR + PI	17	13	76%	9.75*	10	59%		19
	GDR	16	4	25%	(1.98–47.94)	7[a]	44%		
Oude Voshaar *et al.* [16]	GDR + PI	73	33	45%	0.80				23
	GDR	73	37	51%	(0.42–1.54)				
Spiegel *et al.* [30]	GDR + PI	11	9	82%	1.13	9	82%	6.75	32
	GDR	10	8	80%	(0.13–9.94)	4	40%	(0.93–49.23)	
Vorma *et al.* [31]	GDR + PI	39	5	13%	0.4	7	18%	0.46	31
	GDR	37	10	27%	(0.12–1.30)	12	32%	(0.16–1.33)	

GDR plus substitutive pharmacotherapy									
Ashton *et al.* [33]	GDR + buspirone	11	6	55%	0.11	6	55%	0.11	29
	GDR + placebo	12	11	92%	(0.01–1.16)	11	92%	(0.01–1.16)	
Di Costanzo & Rovea [34]	GDR + carbamazepine	18	15	88%	1.43				12
	GDR + placebo	18	14	78%	(0.27–7.55)				
Garfinkel *et al.* [35]	Period 1								
	GDR + melatonin	18	11	61%	4.71*	14	78%	2.10	18
	GDR + placebo	16	4	25%	(1.08–20.63)	10	63%	(0.47–9.44)	
Hantouche [36]	GDR + aspartate	69	55	80%	0.9				23
	GDR + placebo	75	61	81%	(0.39–2.06)				
Lader & Olajide [37]	GDR + buspirone	13	5	38%	0.52				13
	GDR + placebo	11	6	55%	(0.10–2.66)				
Lader *et al.* [38]	GDR + Alpidem	13	4	31%	0.15				13
	GDR + placebo	12	9	75%	(0.03–0.86)				
Mercier-Guyon *et al.* [39]	GDR + captodiamine	40	40	100%	Not estimable				17
	GDR + placebo	41	41	100%					
Morton & Lader [40]	GDR + buspirone	12	6	50%	1.00				12
	GDR + placebo	12	6	50%	(0.20–4.95)				
Nakao *et al.* [41]	GDR + paroxetine	22	10	46%	3.96*				8
	GDR	23	4	17%	(1.01–15.52)				
Rickels *et al.* [18]	GDR + trazodone	41	23	56%	4.58*	16	39%	2.13	18
	GDR + sodium valproate	19	11	58%	(1.35–15.55)[a]	11	58%	(0.67–6.72)[b]	
	GDR + placebo	18	4	22%		5	28%		
Schweizer *et al.* [42]	GDR + carbamazepine	27	18	67%	2.31	14	27%	1.66	19
	GDR + placebo	28	13	46%	(0.77–6.88)	11	37%	(0.57–4.85)	
Tyrer *et al.* [43]	GDR + dothiepin	41	11	27%	0.63				12
	GDR + placebo	46	17	37%	(0.25–1.56)				
Udelman & Udelman [44]	GDR + buspirone	36	21	58%	1.56				19
	GDR + placebo	36	17	47%	(0.62–3.97)				
Zitman & Couvee [45]	GDR + paroxetine	70	32	46%	1.47	7	10%	1.08	24
	GDR + placebo	129	47	36%	(0.81–2.65)	12	9%	(0.41–2.89)	
GDR plus abrupt substitutive (AS) pharmacotherapy									
Cantopher *et al.* [46]	GDR + AS propranolol	15	4	27%	0.17				25
	GDR	16	11	69%	(0.030.78)				
Lemoine *et al.* [47]	GDR + AS cyamemazine	84	63	75%	0.36	56	67%		29
	GDR	84	75	89%	(0.15–0.84)	55	66%		
Abrupt withdrawal (AW) plus AS pharmacotherapy									
Cialdella *et al.* [17]	AW + AS Homeogene	15	10	67%	1.69				11
	AW + AS Sedatif	20	12	60%	(0.60–4.74)				
	AW + placebo	26	13	50%					
GDR plus PI versus AW plus PI									
Sanchez-Craig *et al.* [48]	GDR + PI	23	9	39%	2.14	5	22%	2.62	32
	AW + placebo + PI	19	11	58%	(0.62–7.37)	8	42%	(0.68–10.06)	

*Odds ratios significant, $P < 0.05$. [a]Additional treatment provided control group during follow-up; [b]data collapsed—comparison substitutive pharmacotherapy and gradual reduction. CI: confidence interval; GP: general practitioner; MQS: methodological quality score; OR: odds ratio.

allocated individual patients to conditions randomly [19–21] had a total of 532 participants. They demonstrated that brief interventions to cease benzodiazepine use was more effective than routine care, or not raising the issue at all (OR = 4.37, CI = 2.28–8.40). Two additional studies allocated practices randomly. They also demonstrated that brief interventions were more effective than routine care (OR = 2.21, CI = 1.92–2.55) [22,23].

GDR versus routine care. Only one RCT that met criteria for inclusion in the review directly compared engagement in a programme of GDR of benzodiazepines with routine care [16]. It found that GDR was more effective (OR = 5.96, CI = 2.08–17.11).

Psychological interventions versus routine care. The psychological interventions in these studies involved relaxation training, psychoeducation for benzodiazepine withdrawal or teaching strategies to address insomnia. Three studies totalling 354 participants [16,24,25] compared psychological interventions plus GDR with routine care. This combination of strategies resulted in higher benzodiazepine cessation rates than routine care (OR 3.38, CI = 1.86–6.12). Only one study with 20 participants provided follow-up data [24], which found that benefits of the psychological intervention were maintained (OR = 13.5, CI = 1.20–152.21).

GDR versus GDR plus additional treatment

Twenty-one studies compared the effectiveness of additional treatment to GDR alone. These studies involved either psychological interventions or substitutive pharmacotherapy (Table 3).

GDR plus psychological interventions. Seven studies with 454 participants compared psychological interventions and GDR with GDR alone [16,26–31]. The average reported duration of benzodiazepine withdrawal across studies was 49 days, with a range of 6.5–84 days. Common elements in these psychological interventions were relaxation training, cognitive-behavioural treatment of insomnia, and in the case of multi-component programmes, self-monitoring of consumption and symptoms, goal-setting, management of withdrawal and coping with anxiety.

The addition of psychological interventions was slightly more effective than GDR alone at post-cessation (OR = 1.82, CI = 1.25–2.67), and this effect was maintained at follow-up (six studies, 308 participants, OR = 1.88, CI = 1.19–2.97). Four of the studies demonstrated a favourable OR (58% of studies) [26–29].

Since completion of the meta-analysis, a further study by Belleville *et al.* [32] has been published. That study compared therapist-assisted use of cognitive-behavioural bibliotherapy for insomnia and GDR with GDR alone. On intention to treat, almost identical proportions of participants had ceased medication in each condition at post-treatment (combined: 16 of 28, 57%, GDR: 16 of 25, 64%) and at the 6-month follow-up, cessation rates had fallen to 32% for the combined condition (nine of 28) and 52% (13 of 25) for GDR alone. It would not be appropriate to add that study to the primary meta-analysis, as that would require that the full literature search be reapplied. If it had been included in the analyses, the effect would change to (OR = 1.66, CI = 1.16–2.37) at post-treatment and (OR = 1.50, CI = 0.99–2.28) at follow-up.

GDR plus substitutive pharmacotherapy. Tables 3 and 4 list the substitutive pharmacotherapies and ORs for all included studies. Average duration of benzodiazepine dose reduction was 36 days across studies, with a range of 14–70 days (Table 2). Four substitutive studies did not provide information on duration of the withdrawal period.

The focus in this analysis was on whether the provision of additional medication would result in increased cessation rates when compared with a GDR regimen alone. Fourteen studies with a total of 927 participants compared GDR plus substitutive pharmacotherapy with GDR alone [18,33–45]. There was no additional benefit from substitutive pharmacotherapy at post-cessation (OR = 1.30, CI = 0.97–1.73) or follow-up (five studies, 389 participants, OR = 1.30, CI = 0.77–2.20). Three other studies with 260 participants [17,46,47] found that abrupt substitution of substitutive pharmacotherapy was actually *less* effective than GDR (OR = 0.30, CI = 0.14–0.64), and no more effective than abrupt reduction alone (OR = 1.69, CI = 0.60–4.74). Only three

Table 4 Substitutive pharmacotherapy odds ratios (ORs).

Medication	*OR (95% CI)*
Alpidem [38]	0.15 (0.03–0.86)
Aspartate [36]	0.90 (0.39–2.06)
Buspirone [33,37,40,44]	0.88 (0.46–1.71)
Carbamazepine [34,42]	2.00 (0.80–4.96)
Cyamemazine [47]	0.36 (0.15–0.84)
Dothiepin [43]	0.63 (0.25–1.56)
Homeogene [17]	2.00 (0.53–7.49)
Melatonin [35]	4.71* (1.08–20.63)
Paroxetine [41,45]	1.73* (1.01–2.96)
Propranolol [46]	0.17 (0.03–0.78)
Sedatif [17]	1.50 (0.46–4.88)
Trazodone [18]	4.47* (1.25–15.94)
Valproate [18]	4.81* (1.14–20.25)
Captodiamine [39]	Not estimable

*OR significant, $P < 0.05$. CI: confidence interval.

substitutive pharmacotherapy studies recorded a positive OR (21% of studies). Garkfinkel *et al.* [35] found that administering melatonin in conjunction with GDR was more effective than GDR alone in the management of sleep problems. Nakao [41] found that the addition of paroxetine provided a beneficial effect and Rickels *et al.* [18] showed additive effects from trazodone and valproate.

GDR versus abrupt withdrawal in the context of additional treatment

One study [49] compared a combination of psychological treatment and either gradual reduction or abrupt withdrawal plus placebo. It found no significant difference between these treatments at either post-treatment (OR = 2.14, CI = 0.62–7.37) or follow-up (OR = 2.62, CI = 0.68–10.06). In the absence of further studies, no meta-analysis can be conducted.

Quality of studies

The proportion of studies meeting each of the MQS criteria is outlined in Table 1. Some criteria were met frequently by studies. All had to report the initial number of participants in order to meet the inclusion criterion of intention-to-treat analyses. Almost all also reported proportions that were benzodiazepine-free at post-treatment. Attrition was almost always reported by condition; three-quarters of studies reported at least 70% follow-up rates, 78% reported the initial benzodiazepine dose or duration of use and 85% reported use of a treatment protocol. On the other hand, few studies reported whether participants fulfilled dependence criteria or fully reported potentially co-occurring disorders. Few had fully manualized sessions or independent tests of treatment fidelity; most follow-up periods were less than 12 months and duration of benzodiazepine cessation and extent of treatment outside the study were rarely reported. In only 45% were data collectors blind to condition, and in just 12% were they independent. Table 5 outlines the MQS for each of the intervention approaches. The median MQS was 19, and its mean was 21.0 [standard deviation (SD) = 7.1]. There was no systematic relationship between the MQS and the size of effect. Forty-three per cent of studies with an MQS at or above the median had a significant OR, as did 42% scoring below the median (Table 5), and the correlation between MQS and ORs was not significant (NS) ($r = -0.05$, NS). This result provides confidence in the results from the meta-analyses.

Table 5 Comparisons of quality score and odds ratios.

	MQS	Odds Ratio significant
Comparison of Treatment with Routine Care (RC)		
Brief intervention versus RC		
Individuals randomised		
≥Median	2	1
<Median	1	1
Practices randomised		
≥Median	2	2
Gradual Dose Reduction (GDR) versus RC		
≥Median	1	1
Psychological interventions (PI) versus RC		
≥Median	2	2
<Median	1	1
GDR versus GDR plus additional treatment		
GDR plus PI		
≥Median	7	4
GDR plus substitutive pharmacotherapy		
≥Median	7	0
<Median	10	3
GDR plus PI versus abrupt withdrawal plus PI		
≥Median	1	0
Total*		
≥Median	22	10
<Median	12	5

*Oude Voshaar *et al.* (16) included in three categories.

DISCUSSION

Interpretation of the results

This was the first study to systematically review treatment approaches for cessation of benzodiazepine use solely within general practice and out-patient settings. There was substantial variability in participant numbers, types of treatment and dose reduction regimens. Few studies controlled for potential effects of practitioner expectancies on assessments by having independent, blind assessors, and few had fidelity checks that would assess the extent of contagion between treatment conditions.

However, there are sufficient data to offer some conclusions. Despite a growth in the amount and quality of benzodiazepine interventions and related research over recent years, ongoing difficulties in achieving high rates of benzodiazepine cessation are seen, reflecting the significant challenge that this objective poses. Providing individuals with advice to cease benzodiazepine use or with a more extensive intervention increases cessation rates significantly in comparison with routine care. On data available from the literature search, psychological interventions may provide a small but significant additional benefit over GDR alone at post-cessation and at follow-up. However, a study published after completion of the literature search, using therapist-assisted bibliotherapy, produced negative results [12]. We await further study to determine which psychological intervention is more effective, and whether the intervention has to be delivered face to face in order to make a significant added contribution to cessation.

Only three of the 17 studies using substitutive pharmacotherapy demonstrated greater cessation rates at post-treatment, and no studies showed superiority from substitutive pharmacotherapy at follow-up. Due to the variability in medications and research designs, it was not possible to assess conditions under which substitutive pharmacotherapy provided a better outcome than GDR alone. It is not clear why the existing substitutive pharmacotherapy trials did not achieve more powerful results. The range of treatments was diverse, ranging from ones with multiple active ingredients (e.g. Homeogene®, Sedatif®) to agents that act directly on subclasses of the benzodiazepine receptor (e.g. Alpidem) and others whose mechanism of action is uncertain (e.g. Captodiamine). Given positive effects in single studies on paroxetine hydrochloride and trazadone, it is possible that additional trials of specific existing medications (and of antidepressants in particular) may show stronger effects. Alternatively, it may be that current substitutive therapies do not address completely withdrawal symptoms that are experienced when benzodiazepines are halted abruptly or reduced over a short period, and that new compounds are required. At present, the most conservative conclusion for practitioners is that current evidence is insufficient to support the prescription of adjunctive pharmacotherapy.

A previous meta-analysis by Oude Voshaar *et al.* [10] that used different inclusion and exclusion criteria concurred with our observation that brief intervention was more effective than routine care. Addition of a psychological intervention was also found to provide better results than dose reduction alone. However, in contrast to the current analysis, Oude Voshaar *et al.* [10] concluded that substitutive pharmacotherapy was also slightly more effective than GDR alone. The contrasting results can be attributed primarily to both in-patient and out-patient studies being included in the previous review, and its inclusion of some studies that did not allow calculation of intention-to-treat data.

Limitations to the current study include our reliance on published data and the conservative nature of intention-to-treat data. It is possible that additional studies might have been included, with potential impact on our findings, if unpublished data were included or authors provided intention-to-treat data that were omitted from the published paper. The assumption that those lost to follow-up were still using benzodiazepines may not always have been true. However, we contend that the adopted approach was the most consistent and defensible review strategy.

Future research

Some existing multi-component psychological interventions include aspects to both assist participants to deal with withdrawal symptoms and address symptoms that triggered the person's initial prescription of benzodiazepines (e.g. insomnia [49], anxiety [50] and dysphoria [51].

Effective coverage of these elements may well be critical to success. Further enhancement of the impact of psychological intervention may, potentially, be obtained by using additional strategies from treatment of other addictive disorders. Examples include motivational enhancement [52], cognitive therapy for excessively positive expectancies of benzodiazepines and for misattributions of withdrawal symptoms to the problem that triggered initial prescriptions, identification of specific high-risk situations for lapses, and application of problem-solving to facilitate effective coping [53]. A more comprehensive psychological intervention may have a greater prospect of success in maintaining engagement of participants, and achieving elimination of benzodiazepine use than simple GDR. Future research should examine not only the impact of additional psychological strategies, but also assess which components may be responsible for any added effects of psychological intervention above GDR alone.

A second area requiring research attention is the cost-effectiveness of interventions. We are aware of only one study that examined this issue to date [54]. One potential approach to cessation with potential for cost-effectiveness is to use stepped care [55]. For example, a brief intervention plus GDR might be applied initially, with additional psychological treatment being added only in cases where the low-cost intervention is unsuccessful. Provided that further research does not replicate the relatively poor outcomes from assisted bibliotherapy in Belleville *et al.* [32], initial psychological intervention might be provided effectively at low cost via self-help manuals [56,57], mailed treatments [58], the internet or CD-ROM [59], which in other problem domains have produced results approaching those from face-to-face treatments [60,61]. More expensive face-to-face treatments might then focus upon those who do not respond to remotely delivered intervention, or whose features suggest that face-to-face treatment may be needed. However, such an approach awaits examination in controlled research designs and related economic analyses. It would also need to address effects on the self-efficacy and motivation of both patients and practitioners when more intervention is required.

A third area of potential research focus is the design of withdrawal regimens. For example, it is not currently possible to determine the ideal period over which a withdrawal regimen should be completed, as several studies did not provide that information or used a range of periods. Studies that compare systematically durations of GDR are required.

CONCLUSIONS

Evidence for the use of substitutive pharmacotherapy in the management of benzodiazepine dependence remains relatively weak. However, raising the issue of cessation of benzodiazepine use systematically with every patient who has been prescribed benzodiazepines for longer than 3 months and recommending that they gradually reduce the benzodiazepine dosage is likely to result in better cessation rates when compared with continuation of routine care. Linking patients with psychological assistance may further increase the chances of ceasing use successfully.

Declarations of interest

None.

References

1. Griffiths R. R., Weerts E. M. Benzodiazepine self-administration in humans and laboratory animals: implications for problems of long-term use and abuse. *Psychopharmacology* 1997; **134**: 1–37.
2. Holden J. D., Hughes I. M., Tree A. Benzodiazepine prescribing and withdrawal for 3234 patients in 15 general practices. *Fam Pract* 1994; **11**: 358–62.
3. Australian Bureau of Statistics. *National Health Survey, First Results, Australia, 1995*. Canberra: Australian Bureau of Statistics; 1996.
4. Parr J. M., Kavanagh D. J., Young R. M., McCafferty K. Views of general practitioners and benzodiazepine users on benzodiazepines: a qualitative analysis. *Soc Sci Med* 2006; **62**: 1237–49.
5. Tyrer P., Murphy S., Riley P. The benzodiazepine withdrawal symptom questionnaire. *J Affect Disord* 1990; **19**: 53–61.
6. Cormack M. A., Owens R. G., Dewey M. E. The effect of minimal interventions by general practitioners on long-term benzodiazepine use. *J R Coll Gen Pract* 1989; **39**: 408–11.
7. Hopkins D. R., Sethi K. B., Mucklow J. C. Benzodiazepine withdrawal in general practice. *J R Coll Gen Pract* 1982; **32**: 758–62.
8. Rickels K., Case W. G., Schweizer E., Garcia-Espana F., Fridman R. Benzodiazepine dependence: management of discontinuation. *Psychopharmacol Bull* 1990; **26**: 63–8.
9. Cormack M. A., Sinnott A. Psychological alternatives to long-term benzodiazepine use. *J R Coll Gen Pract* 1983; **33**: 279–81.
10. Oude Voshaar R. C., Couvee J. E., van Balkom A. J., Mulder P. G., Zitman F. G. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry* 2006; **189**: 213–20.
11. Denis C., Fatseas M., Lavie E., Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database Syst Rev* 2006; **3**: CD005194.
12. Begg C., Cho M., Eastwood S., Horton R., Moher D., Olkin I. *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276**: 637–9.
13. Moyer A., Finney J. W., Swearingen C. E. Methodological characteristics and quality of alcohol treatment outcome studies, 1970–98: an expanded evaluation. *Addiction* 2002; **97**: 253–63.
14. Miller W. R., Wilbourne P. L. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 2002; **97**: 265–77.
15. Review Manager (RevMan) [computer program]. *Version 4.2 for Windows edn*. Copenhagen: The Cochrane Collaboration/The Nordic Cochrane Centre; 2003.
16. Oude Voshaar R. C., Gorgels W. J. M. J., Mol A. J. J., Van Balkom A. J. L. M., Van de Lisdonk E. H., Breteler M. H. M. *et al.* Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-conditioned, randomised controlled trial. *Br J Psychiatry* 2003; **182**: 498–504.
17. Cialdella P., Boissel J. P., Belon P. Homeopathic specialties as substitutes for benzodiazepines: double-blind vs. placebo study. *Therapie* 2001; **56**: 397–402.
18. Rickels K., Schweizer E., Garcia Espana F., Case G., DeMartinis N., Greenblatt D. *et al.* Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology* 1999; **141**: 1–5.
19. Bashir K., King M., Ashworth M. Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines. *Br J Gen Pract* 1994; **44**: 408–12.
20. Heather N., Bowie A., Ashton H., McAvoy B., Spencer I., Brodie J. *et al.* Randomised controlled trial of two brief interventions against long-term benzodiazepine use: outcome of intervention. *Addict Res Theory* 2004; **12**: 141–54.
21. Vicens C., Fiol F., Llobera J., Campoamor F., Mateu C., Alegret S. *et al.* Withdrawal from long-term benzodiazepine use: randomised trial in family practice. *Br J Gen Pract* 2006; **56**: 958–63.
22. Gorgels W. J. M. J., Oude-Voshaar R. C., Mol A. J. J., van de Lisdonk E. H., van Balkom A. J. L. M., van den Hoogen H. J. M. *et al.* Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drug Alcohol Depend* 2005; **78**: 49–56.
23. Niessen W. J., Stewart R. E., Broer J., Haaijer-Ruskamp F. M. Reduction in the consumption of benzodiazepines due to a letter to chronic users from their own general practitioner. *Ned Tijdschr Geneeskd* 2005; **149**: 356–61.
24. Giblin M. J., Clift A. D. Sleep without drugs. *J R Coll Gen Pract* 1983; **33**: 628–33.
25. Jones D. Weaning elderly patients off psychotropic drugs in general practice: a randomised control trial. *Health Trends* 1990; **22**: 164–6.
26. Baillargeon L., Landreville P., Verreault R., Beauchemin J.-P., Gragoire J.-P., Morin C. M. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *Can Med Assoc J* 2003; **169**: 1015–20.
27. Gosselin P., Ladouceur R., Morin C. M., Dugas M. J., Baillargeon L. Benzodiazepine discontinuation among adults with GAD: a randomized trial of cognitive-behavioral therapy. *J Consult Clin Psychol* 2006; **74**: 908–19.
28. Morin C. M., Bastien C., Guay B., Radouco-Thomas M., Leblanc J., Vallieres A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 2004; **161**: 332–42.

29. Otto M. W., Pollack M. H., Sachs G. S., Reiter S. R., Melzer-Brody S., Rosenbaum J. F. Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. *Am J Psychiatry* 1993; **150**: 1485–90.
30. Spiegel D. A., Bruce T. J., Gregg S. F., Nuzzarello A. Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? *Am J Psychiatry* 1994; **151**: 876–81.
31. Vorma H., Naukkarinen H., Sarna S., Kuoppasalmi K. Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. *Addiction* 2002; **97**: 851–9.
32. Belleville G., Guay C., Guay B., Morin C. M. Hypnotic taper with or without self-help treatment of insomnia: a randomized clinical trial. *J Consult Clin Psychol* 2007; **75**: 325–35.
33. Ashton C. H., Rawlins M. D., Tyrer S. P. A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. *Br J Psychiatry* 1990; **157**: 232–8.
34. Di Costanzo E., Rovea A. The prophylaxis of benzodiazepine withdrawal syndrome in the elderly: the effectiveness of carbamazepine. Double-blind study v. placebo. *Minerva Psychiatr* 1992; **33**: 301–4.
35. Garfinkel D., Zisapel N., Wainstein J., Laudon M. Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999; **159**: 2456–60.
36. Hantouche E. G., Guelfi J. D., Comet D. Discontinuation of long-term benzodiazepine use: double-blind controlled study of L-aspartate magnesium versus placebo in 144 chronic users of BZD. *Encephale* 1998; **24**: 469–79.
37. Lader M., Olajide D. A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. *J Clin Psychopharmacol* 1987; **7**: 11–5.
38. Lader M., Farr I., Morton S. A comparison of alpidem and placebo in relieving benzodiazepine withdrawal symptoms. *Int Clin Psychopharmacol* 1993; **8**: 31–6.
39. Mercier Guyon C., Chabannes J. P., Saviuc P. The role of captodiamine in the withdrawal from long-term benzodiazepine treatment. *Curr Med Res Opin* 2004; **20**: 1347–55.
40. Morton S., Lader M. Buspirone treatment as an aid to benzodiazepine withdrawal. *J Psychopharmacol* 1995; **9**: 331–5.
41. Nakao M., Takeuchi T., Nomura K., Teramoto T., Yano E. Clinical application of paroxetine for tapering benzodiazepine use in non-major-depressive outpatients visiting an internal medicine clinic. *Psychiatry Clin Neurosci* 2006; **60**: 605–10.
42. Schweizer E., Rickels K., Case W. G., Greenblatt D. J. Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; **48**: 448–52.
43. Tyrer P., Ferguson B., Hallstrom C., Michie M., Tyrer S., Cooper S. *et al.* A controlled trial of dothiepin and placebo in treating benzodiazepine withdrawal symptoms. *Br J Psychiatry* 1996; **168**: 457–61.
44. Udelman H. D., Udelman D. L. Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. *J Clin Psychiatry* 1990; **51** (Suppl.): 46–50.
45. Zitman F. G., Couvee J. E. Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off: report on behalf of the Dutch chronic benzodiazepine working group. *Br J Psychiatry* 2001; **178**: 317–24.
46. Cantopher T., Olivieri S., Cleave N., Edwards J. G. Chronic benzodiazepine dependence. A comparative study of abrupt withdrawal under propranolol cover versus gradual withdrawal. *Br J Psychiatry* 1990; **156**: 406–11.
47. Lemoine P., Kermadi I., Garcia-Acosta S., Garay R. P., Dib M. Double-blind, comparative study of cyamemazine vs. bromazepam in the benzodiazepine withdrawal syndrome. *Prog NeuroPsychopharmacol Biol Psychiatry* 2006; **30**: 131–7.
48. Sanchez Craig M., Cappell H., Busto U., Kay G. Cognitive-behavioural treatment for benzodiazepine dependence: a comparison of gradual versus abrupt cessation of drug intake. *Br J Addict* 1987; **82**: 1317–27.
49. Lichstein K. L., Riedel B. W. Behavioral assessment and treatment of insomnia: a review with an emphasis on clinical application. *Behav Ther* 1994; **25**: 659–88.
50. Durham R. C., Allan T. Psychological treatment of generalised anxiety disorder: a review of the clinical significance of results in outcome studies since 1980. *Br J Psychiatry* 1993; **163**: 19–26.
51. Persons J. B. Indications for psychotherapy in the treatment of depression. *Psychiatr Ann* 1998; **28**: 80–3.
52. Miller W. R., Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford Press; 1991
53. Marlatt G. A., George WH. Relapse prevention: introduction and overview of the model. *Addiction Biology* 1984; **79**: 261–73.
54. Oude Voshaar R. C., Krabbe P. F. M., Gorgels W. J. M. J., Adang E. M. M., van Balkom A. J. L. M., van de Lisdonk E. H. *et al.* Tapering off benzodiazepines in long-term users: an economic evaluation. *Pharmacoeconomics* 2006; **24**: 683–94.
55. Lader M., Russell J. Guidelines for the prevention and treatment of benzodiazepine dependence: summary of a report from the Mental Health Foundation. *Addiction* 1993; **88**: 1707–8.
56. Glasgow R. E., Swaney K., Schafer L. Self-help manuals for the control of nervous habits: a comparative investigation. *Behav Ther* 1981; **12**: 177–84.
57. Wright J., Clum G. A., Roodman A., Febbraro G. A. M. A bibliotherapy approach to relapse prevention in individuals with panic attacks. *J Anxiety Disord* 2000; **14**: 483–99.
58. Sitharthan T., Kavanagh D. J., Sayer G. Moderating drinking by correspondence: an evaluation of a new method of intervention. *Addiction* 1996; **91**: 345–55.
59. Stroem L., Pettersson R., Andersson G. A controlled trial of self-help treatment of recurrent headache conducted via the Internet. *J Consult Clin Psychol* 2000; **68**: 722–7.
60. Ghosh A., Marks I. M., Carr A. C. Therapist contact and outcome of self-exposure treatment for phobias: a controlled study. *Br J Psychiatry* 1988; **152**: 234–8.
61. Lidren D. M., Watkins P. L., Gould R. A., Clum G. A., Asterino M., Tulloch H. L. A comparison of bibliotherapy and group therapy in the treatment of panic disorder. *J Consult Clin Psychol* 1994; **62**: 865–9.

