Feasibility and effectiveness of deprescribing benzodiazepines and Z-drugs; systematic review and meta-analysis.

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Running head: Deprescribing benzodiazepines and Z-drugs

Word count: 3480

Declarations of competing interest: None. The authors have declared no competing interests.

Funding: None.

Ethical approval: Not applicable.

ABSTRACT

Background and Aims

2.4 million adults in England were dispensed a benzodiazepine or Z-drug (BZRA) in 2017/18, and more than 250,000 patients in the UK take BZRAs beyond the recommended duration. Deprescribing is a clinician-guided process of withdrawing inappropriate drugs. This review aims to evaluate the evidence-base supporting the feasibility and clinical effectiveness of all-forms of deprescribing initiatives used to discontinue long-term (≥4 weeks) BZRAs.

Method

Systematic review of randomised controlled trials evaluating ~~successful~~ BZRAs deprescribing amongst adults in community, primary or outpatient settings. MEDLINE, Embase and PsycINFO were searched from inception to February 2021. Primary outcomes were successful discontinuation in the short-term (<4 weeks) or long-term (≥4 weeks) and the occurrence of withdrawal symptoms, behavioural or psychological symptoms. Studies were categorised as pharmacological or non-pharmacological supported interventions. Study quality was assessed using the Cochrane risk of bias tool. Where appropriate, risk ratios (RRs), mean differences and 95% confidence intervals (CIs) were calculated, and Mantel-Haenszel methods using the random-effect meta-analysis was undertaken to calculate summary effect estimates.

Results

10 studies were included (n=1431 participants). Heterogeneity in study design and effect was observed. Benzodiazepines were successfully deprescribed when gradually tapered *with* non-pharmacological support compared to gradual tapering alone in the *short-term* (n=124; RR 2.02; 95%CI 1.41, 2.89), and *long-term* (n=123; RR 2.45; 95%CI 1.56, 3.85). Benzodiazepine deprescribing was more successful when supported by non-pharmacological methods versus routine care (n=189; RR 3.26; 95%CI 2.36, 4.51). Quality of evidence reporting effectiveness was very low to low.

Conclusions

Findings indicate it may be feasible to deprescribe benzodiazepines in the short and long-term depending on the process and support mechanisms employed. More robust trials evaluating BZRA deprescribing with clinical effectiveness outcomes are required. Realist and qualitative methods are suggested to unpick the complexities and determinants of deprescribing.

Keywords

Deprescribing; systematic review; meta-analysis; benzodiazepines; Z-drugs

INTRODUCTION

When first introduced benzodiazepines were met with enthusiasm as an alternative to barbiturates which were known to have poor side effect profiles, leading to a worldwide rise in prescribing.[1,2] However, soon enough there were rising concerns towards over-prescription, dependency with long-term use and withdrawal reactions (e.g. excitability, anxiety, pain, fatigue) upon discontinuation with the physical and psychological symptoms associated with long-term benzodiazepine-use becoming well documented.[1–5] Now benzodiazepines are indicated for short-term use for several indications including sleep disorders, anxiety, seizures and muscle relaxation ~~anxiety insomnia~~.[1,6]

Z-drugs are non-benzodiazepine drugs that have hypnotic properties, indicated for the short-term management of insomnia.[6] Similarly to benzodiazepines, concerns with the potential for Z-drugs to cause tolerance, dependence and withdrawal symptoms have led to their restricted use.[7]

BZRA usage data between countries is heterogenous. A prevalence of BZRA use for more than 6 months in the general population has been estimated to range between 6-15% and vary between countries.[8] The Organisation for Economic Co-operation and Development (OECD) reported amongst 12 countries in 2019 that elderly patients (≥65 years) with a prescription for chronic benzodiazepine or related drugs ranged from 2.7 defined daily dose (DDDs) per 1000 population in Australia to 103.4 DDDs per 1000 population in Iceland.[9] In England, approximately 2.4 million adults were dispensed a BZRA in 2017/18 and more than 250,000 patients in the UK take BZRAs far beyond the recommended duration.[10,11] The ongoing issue of long-term BZRAs has continued and it can therefore be postulated that appropriate discontinuation of these medicines is a clinical priority.

Deprescribing is the clinical process of withdrawing inappropriate medication.[12] A variety of deprescribing methods have been described including pharmacological interventions, abrupt or gradual tapering, substitution and non-pharmacological support therapies e.g. cognitive behavioural therapy (CBT).[3,13–15]

Previous reviews that have evaluated the effectiveness of deprescribing have not specifically evaluated BZRAs.[16,17] Systematic reviews have sought to evaluate the deprescription of psychotropic drugs but their utility is limited by their search strategies, select populations and heterogenous outcomes thereby preventing primary care clinicians from applying the evidence

in practice.[18–21] Recently a review reported that brief interventions in primary care, which encompassed oral or written communication, on the reduction or discontinuation of long-term BZRAs use for ≥3 months are more effective than usual care.[8]

Multiple barriers to successful deprescribing interventions exist including professional, patient (social) and system factors.[22–25] At the professional level, uncertainty, skill and knowledge gaps about the effectiveness and feasibility of deprescribing long-term BZRAs can lead to reluctance to deprescribe with clinicians reporting a lack of clear evidence base to support practice.[22,24,25] Prescribers report fear of negative consequences of deprescribing such as withdrawal symptoms, symptom recurrence and poorer quality of life.[25] This review therefore aims to review the existing body of evidence in a broader sense, rather than brief, discrete interventions. It will appraise the evidence base assessing whether feasible and positive outcomes through deprescribing BZRAs can be achieved, consequently addressing the clinician uncertainty barrier in the deprescribing process.

There is ambiguity in the definition of what long-term use of BZRAs is, with studies defining and reporting "long-term" benzodiazepine use from one month to several years despite guidance for the use Z-drugs to be limited to the short duration of 2-4 weeks.[7,26] On this basis this review defined long-term BZRA use as 4 weeks or more, and was concerned with the complete discontinuation of a BZRA-use as a primary end point in order to directly answer the question on feasibility and minimise uncertainty for prescribing clinicians. Interventions in the community were evaluated, including outpatients and nursing homes, as chronic medications are predominantly managed in the community where clinicians have a key role in their prescribing process.

Aims and objectives

A systematic review and meta-analysis was undertaken which aimed to evaluate the evidence-base supporting the feasibility and clinical effectiveness of all-forms of deprescribing initiatives used to discontinue long-term BZRA in the community setting.

The objectives were to:

1. Evaluate the feasibility of deprescribing interventions for long-term BZRA use in terms of the pre-determined primary outcomes
2. Evaluate the clinical effectiveness of deprescribing interventions for long-term BZRA use in terms of the pre-determined primary and secondary outcomes
3. Evaluate the risk of bias

4. Categorise deprescribing interventions into pharmacological or non-pharmacological support, and then to sub-categorise by shared comparator arms

METHOD

A systematic search of the literature was conducted. The primary research question and analysis plan were not pre-registered on a publicly available platform.

Study Inclusion Criteria

Types of studies: Patient and cluster randomised controlled trials (RCTs) were included to reduce the risk of confounding and selection bias.[27] For individual-RCTs, any number of intervention and control arms were accepted. For cluster-RCTs, only studies with at least two intervention sites and two control sites were accepted to avoid bias arising from the intervention in a single comparator site being completely confounded by a study site.[28] Studies limited to humans and published in the English language were included.

Participants: Adults aged 18 years or older who were taking at least one long-term BZRA that was not clinically indicated or wanted by the patient. To increase the generalisability of the review findings, participants could use any type of BZRA, at any dose and indication so long as the same BZRA was being used throughout. While the use of other non-BZRA drugs with psychoactive properties could influence and confound the effect size of the intervention, it was not stipulated as an exclusion criterion because the exclusivity of using a RCT-study design ought to balance such confounders, furthermore this restriction would reduce the generalisability of the findings. As midazolam is indicated only for the acute management of seizures, peri-operative management and for symptom management in palliative care it was the only BZRA to be excluded in this review.[6] Settings included community, primary or outpatient care.

Intervention: deprescription of at least one regular long-term BZRA (use for 4 weeks or more) that no longer had an indication to continue, for an example resolution of the condition(s) that the BZRA was originally indicated for. Any of the following methods of drug withdrawal were accepted:

- Pharmacological supportive therapy using a substitute drug that was available on the UK market, by referring to the British National Formulary (BNF).[6]

- Non-pharmacological therapy with any form of psychological supportive therapy.

Within these categories, BZRA deprescription by gradual tapering (GT) or abrupt withdrawal were both accepted. Dose reductions without drug discontinuation and studies that evaluated the deprescription of psychoactive drugs in general were excluded. Studies evaluating pharmacological supportive therapy with drugs that were withdrawn from the market or under investigation were also excluded. Exclusive evaluation of the intervention in pregnancy, palliative care, or drug and alcohol detoxification were excluded.

Comparator: Any comparator was accepted including the continuation of the same or different BZRA, placebo therapy or substitute therapy (either pharmacological or non-pharmacological). Where the intervention involved switching the BZRA to another then this must have applied to all participants in the comparator arm.

Outcomes: The following outcomes were stipulated to reflect clinically meaningful measures that are significant to patients and clinicians. Included studies must have planned and reported one or more of these outcomes.

Primary outcomes were:

(1.1) Successful withdrawal from BZRA(s) over the:

a) short-term (＜4 weeks from intervention completion); and

b) long-term (≧4 weeks from intervention completion).

Successful drug withdrawal was defined as discontinuation at follow-up, determined by biochemical or self-reported methods. The use of prescription data as a surrogate for BZRA usage was excluded to avoid misclassification.

(1.2) Withdrawal symptoms measured by the validated Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) following completion of the intervention and compared to the baseline.

(1.3) Behavioural or psychological symptoms, for which the BZRA is licensed to manage, measured with a validated scale following completion of the intervention and compared to the baseline.

Secondary outcomes were (2.1) mortality, (2.2) global function, (2.3) quality of life (QoL), and (2.4) psychomotor function using a validated scale. This was compared between participants who had BZRAs deprescribed against those who had BZRAs continued.

Search strategy

MEDLINE, Embase and PsycINFO databases were searched from inception to February 2021. Citation searching from systematic reviews acquired in the literature search was also completed.

Indexed and free-text terms for 'deprescribing' were combined with a list of identified individual generic, branded and chemical names.[3,6,29] Published search restrictions to RCTs were applied.[30,31] A full search strategy is available in Supporting information, Table S1. All titles and abstracts were screened by two independent researchers using DistillerSR, before retrieving full-texts for review.[32] Any differences were resolved by consensus in the first instance, otherwise a third researcher provided a final decision.

Data collection and quality assessment

Data extraction was completed using a pre-specified form, sourced from The Effective Practice and Organisation of Care (*EPOC*) Group, that collected details on study design, quality and outcomes.[33,34] The risk of bias for each study was assessed by two independent reviewers against the Cochrane risk of bias tool with any differences being resolved by consensus.[33]

Data analysis

Cluster-RCTs were only included in a meta-analysis if the study adjusted for data clustering by calculating an intraclass correlation coefficient. Where a study had several follow-up periods, data was segregated into short-term and long-term outcome data or the longest follow-up was selected.[33] Where multiple trial arms were reported only the relevant arms were included.[33]

Studies were categorised by the intervention, pharmacological or non-pharmacological support, and sub-categorised by shared comparator arms. Risk ratios (RRs) and associated 95% confidence intervals (CIs) were calculated for dichotomous data using RevMan v5.3.[35]

Mean differences and respective 95%CIs were calculated for continuous data. Where available median differences were calculated and interquartile ranges (IQRs) at baseline and follow-up were noted.

A meta-analysis was undertaken where studies' intervention and participants were similar. A summary effect estimate was calculated as a weighted average of the intervention effect estimates for the individual studies using RevMan v5.3.[35] Mantel-Haenszel (M-H) methods using the random-effect meta-analysis was used and heterogeneity was assessed by the I^2 statistic.[35] The certainty of the evidence was assessed using the GRADE approach to supplement the summary of findings.[33]

RESULTS

Study identification

1272 results were screened by title and abstract, 116 full-text articles were reviewed, and 10 studies (participants, n =1431) met the inclusion criteria (Figure 1).

[insert figure 1 here]

Figure 1. PRISMA flow diagram of included studies.[36]

Study characteristics

Supporting information, Table S2 summarises the included studies. Where reported, participants had a mean age of 56.7 years (n=553) and 65.4% were female (n=1420). Five studies evaluated deprescribing with non-pharmacological supportive therapies ~~with either CBT or non-specific supportive therapies~~.[37–41] Non-pharmacological supportive therapies included educational consultations comprising of verbal and material information on benzodiazepines and reassurance on deprescribing them, or CBT which could have comprised of behavioural, cognitive, and educational components.

Five studies evaluated deprescribing methods with pharmacological supportive therapies; melatonin, paroxetine or by converting the pre-study BZRA to another BZRA.[42–46] Of the ten studies, five reported that the main indication(s) for the BZRA (s) were insomnia, anxiety and depression.[37–39,41,44]

While no two studies had the same tapering plan, they all weaned the BZRA gradually with incremental dose reductions ranging from 10% to 50%, over the total course of 4 to 12 weeks. The follow-up period ranged from immediately post intervention to 12 months. Control arms included abrupt discontinuation, GT withdrawal or no change with routine clinical care.

One study included participants taking Z-drugs.[44] Six studies excluded participants with a severe psychiatric disorder.[37,38,41,43,44,46] Five studies did not report the indications for the BZRA.[40,42,43,45,46] Two studies excluded participants using other psychoactive drugs.[42,45]

Risk of Bias in Included Studies

The risk of bias varied between the studies (Figure 2 and Supporting information, Figure S1). 90% of studies were assessed as unclear or high risk of bias and no study could be described as free of reporting bias and potentially all the studies carried other forms of bias. Participant use of non-benzodiazepine drugs that might attenuate the intervention was unaccounted for in 8 studies.[37–41,43,44,46]

[insert figure 2 here]

Figure 2: Risk of bias summary for each study

Effects of Interventions

1. Primary Outcomes

Nine studies evaluated successful withdrawal from BZRAs (Table 1).

[insert table 1 here]

Table 1: Summary of findings from the included studies for the primary outcome 1.1 'successful withdrawal from BZRA(s) over the short and long term', sub-categorised by the intervention and comparator type.

1.1.a Successful withdrawal from BZRA(s) over the short-term

Five studies reported this outcome, but variable comparators prevented combination of all five studies in a single meta-analysis. Figure 3 therefore shows combined data from two studies, that compare the deprescription of benzodiazepine(s) with non-pharmacological supportive

measures against deprescribing alone (n=124; RR 2.02; 95%CI 1.41, 2.89; I^2 0%; moderate certainty of evidence).[37,39] Supporting information, Figure S2 shows combined outcome data from three studies, comparing deprescribing BZRA with pharmacological supportive measures against deprescribing alone (n=257; RR 1.06; 95%CI 0.74, 1.50; I^2 71%; low certainty of evidence).[44–46]

[insert figure 3 here]

Figure 3 Forest plot of comparison. Deprescribing by GT alone versus deprescribing by GT and non-pharmacological support: dichotomous data, analysis method RR, outcome: 1.1a successful withdrawal from BZRA(s) over the short-term

1.1.b Successful withdrawal from BZRA(s) over the long-term

Seven studies reported this outcome. Figure 4 shows combined data from three studies comparing deprescribing benzodiazepine(s) with non-pharmacological supportive measures against routine clinical care (n=189; RR 3.26; 95%CI 2.36, 4.51; I^2 0%; moderate certainty of evidence).[38,40,41] Supporting information, Figure S3 shows combined outcome data from two studies comparing deprescribing benzodiazepine(s) with non-pharmacological supportive measures against deprescribing alone (n=123; RR 2.45; 95%CI 1.56, 3.85; I^2 0%; moderate certainty of evidence).[37,39]

[insert figure 4 here]

Figure 4 Forest plot of comparison. Continuation with routine clinical care versus deprescribing by GT and non-pharmacological support: dichotomous data, analysis method RR, outcome: 1.1b successful withdrawal from BZRA(s) over the long-term.

Two studies could not be included in a meta-analysis due to differences in the intervention.[42,44] Summary of study findings and certainty of evidence are provided in Supporting information, Table S3.

1.2 Withdrawal symptoms following completion of the intervention

Two studies reported withdrawal symptoms following the intervention.[40,44] Data synthesis and meta-analysis could not be performed due the difference in study interventions and comparison groups. Supporting information, Table S4 provides summary statistics and certainty of evidence.

1.3 Behavioural or psychological symptoms following completion of the intervention

Three studies reported behavioural or psychological symptoms.[39–41] Data synthesis and meta-analysis could not be performed due to the variation in symptoms reported and the use of different validated scales. Supporting information, Table S4 provides summary statistics and certainty of evidence.

2. Secondary outcomes

None of the included studies assessed secondary outcomes (2.1) mortality; (2.3) QoL; or (2.4) psychomotor function. Only one study reported on the outcome (2.2) global function.[43] Supporting information, Table S4 provides summary statistics and certainty of evidence.

DISCUSSION

This review identified ten studies that evaluated the feasibility or effectiveness of deprescribing long-term BZRAs in community, primary or outpatient care settings. Of the ten studies, nine evaluated feasibility of benzodiazepine deprescription by assessing their successful withdrawal over the short or long-term. Only one included study evaluated Z-drugs, which limits the reviews findings to benzodiazepines.

Heterogenous intervention and comparator arms required multiple pooled effect estimates of smaller groups of studies to be calculated. Where pooled effect estimates were possible, the review showed that:

1) Deprescribing benzodiazepines with GT *with nonpharmacological support* was more successful than gradual deprescribing alone in the short term (n=124; RR 2.02; 95%CI 1.41, 2.89; I^2 0%; moderate certainty of evidence) and long term (n=123; RR 2.45; 95%CI 1.56, 3.85; I^2 0%; moderate certainty of evidence).
2) Deprescribing benzodiazepines with GT *with nonpharmacological support* was more successful than routine clinical care in the long-term (n=189; RR 3.26; 95%CI 2.36, 4.51; I^2 0%; moderate certainty of evidence).
3) It is uncertain if additional pharmacological support with melatonin or paroxetine, or by converting a long-term benzodiazepine to another, leads to successful benzodiazepine-deprescription.

This is consistent with previous research that targeted interventions are more effective than routine care and that non-pharmacological supportive therapies may provide additional benefit over GT alone.[20,47] This review is the first to confirm and extend these conclusions through a systematic review and meta-analysis. This review also challenges previous conclusions suggesting BZRA discontinuation was more successful when undertaken with pharmacological support compared to without.[47] Instead current findings concur that there is insufficient evidence to endorse pharmacological-supportive therapies for deprescribing long-term benzodiazepines.[18,20] This may be explained by the inclusion of fewer studies evaluating pharmacological-supported deprescribing in this review due to stricter pre-specified inclusion and exclusion criteria.

With respect to clinical effectiveness of deprescribing long-term BZRAs in community, primary or outpatient care settings this review found insufficient reported data. There was inconclusive evidence to confirm the impact of deprescribing benzodiazepines upon withdrawal effects, behavioural/psychological symptoms, and global function. It remains uncertain whether deprescribing benzodiazepines influences mortality, QoL and cognitive or psychomotor function. With the inclusion of only one study evaluating Z-drugs, it remains uncertain whether it is feasible and clinically effective to deprescribe Z-drugs.[44]

This is the first systematic review and meta-analysis to evaluate the feasibility and effectiveness of deprescribing long-term BZRAs in community, primary or outpatient care settings. Our findings resonate, extend, and clarify previous narrative reviews and offer robust data supporting the feasibility of deprescribing chronic benzodiazepines drugs in the short and long-term depending on the methods and support applied. Insomnia, anxiety and depression were cited as the main indications for which BZRAs were initiated; findings from this review should therefore be generalised to this cohort.

Limitations to our findings, also highlighted in previous reviews, result from the heterogeneity studies with respect to study design and quality, study methodology such as interventions applied and recruited study populations.[16–20,47–49] The inclusion of RCTs minimised confounding and selection bias, but the included studies were small and heterogenous. Studies were often poorly designed by a lack of control for alternative psychoactive drugs, chosen methods of outcome measurement (i.e. variable follow-up times and definitions of successful deprescription) and inconsistent deprescription plans. Including any type of comparator arm highlights the variation in deprescribing methods. The methodological quality

of the included studies was mixed and overall, there was an unclear or high risk of reporting bias. Detection bias and performance bias was found to affect over half of the included studies, which given the nature of the intervention and occurrence of withdrawal events, was expected. Attrition bias was found to be high risk or unclear in 50% of included studies, with significant losses to follow-up. This limited study power, and only 3 included studies had a low loss to follow-up. This is similar to previous deprescribing reviews which found there were few well-powered RCTs published which assess health outcomes.[17,48] Furthermore, majority of studies excluded participants with any form of severe psychiatric disorder, which limits the generalisability. The significant heterogeneity in the study populations recruited presented as a challenge to synthesising data, descriptively and statistically, and could limit the generalisability of the review's findings.

The use of a systematic review methodology presents limitations to tackle this broader clinical question of how to reduce BZRA use. Deprescribing is complex and multifaceted clinical intervention, affected by patients' variable capacity, perspective and motivation.[50,51] While this review did not intend to elucidate findings by individual drug, indication or regimen, it did find that participants took these for various indications and used assorted regimens. The review also found that few studies accounted for psychiatric health status, concomitant psychoactive drugs, experience of the professionals supporting deprescribing, patient education or previous withdrawal attempts. Realist synthesis methods would describe the logic model with respect to complex interventions and better articulate how these factors might modify feasibility, effectiveness and impact of deprescribing.[52] Qualitative evaluation methods would lend itself to understanding of implementation in practice.[52,53]

CONCLUSION

This review sought to identify whether evidence supports clinicians in deprescribing BZRA through addressing concerns and clinician-uncertainty about feasibility and clinical effectiveness.

Current findings indicate that it may be feasible to deprescribe chronic benzodiazepines drugs in the short and long-term but this is dependent on the methods and support applied, and uncertainty still remains due to the limitations of reported data.

Whilst there is insufficient data to support a meta-analysis of broader clinical effects (e.g. occurrence of withdrawal symptoms, return of symptoms, impact on mortality, global function,

quality of life and psychomotor function) the observation that successful withdrawal is possible suggests that a mixed approach to deprescribing may be the policy to pursue.

Our data provides support to service providers that want to achieve long-term benzodiazepine reduction and suggests investments in *nonpharmacological support* approaches to use alongside deprescribing measures.

Ongoing research needs to better understand BZRA withdrawal for patients as a complex intervention with multiple component parts, variably applied depending on context and so requiring multifaceted approaches to evaluation.[53]

Deprescribing methods need to be actioned on an individualised basis through patient-clinician partnerships with alongside consideration to patient variables, treatment goals and availability of supportive resources, in addition to practical algorithms available.[54]

We conclude that deprescribing long-term benzodiazepines may be viable but there is a need to explore alternative complex approaches to deprescribing. While these alternative complex approaches are beyond the scope of this work, our work may provide an initial basis for mapping out the various complex approaches possible. This review not only provides value to clinicians, but also to the methodological improvement of future studies.

Acknowledgements

The authors would like to thank Dr James Bennett, GP Fellow, for his support in running the search strategy.

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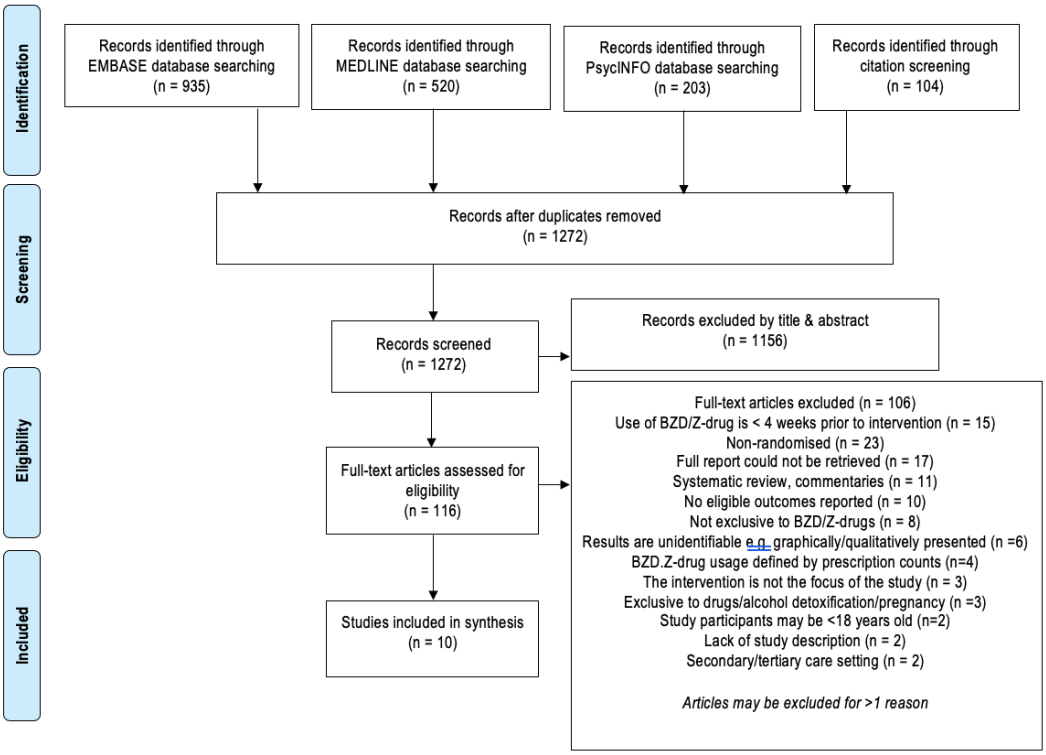

Figure 1. PRISMA flow diagram of included studies.[36]

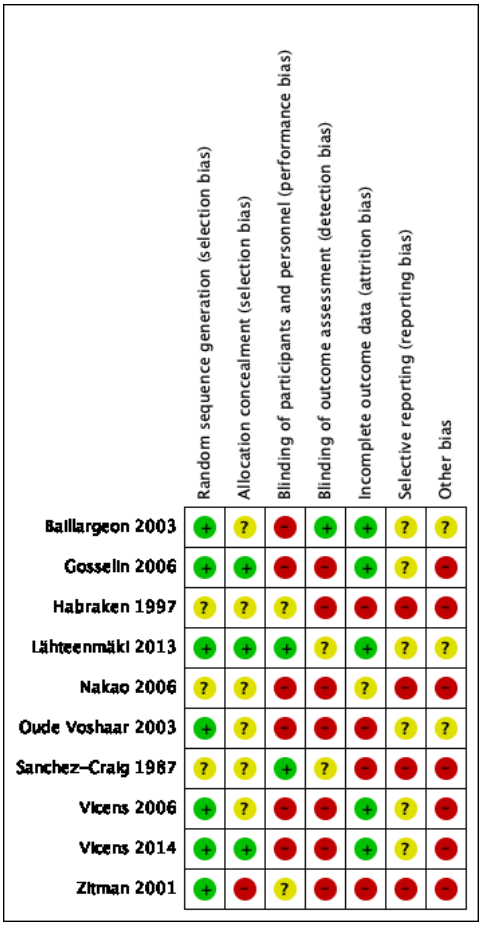

Figure 2: Risk of bias summary for each study

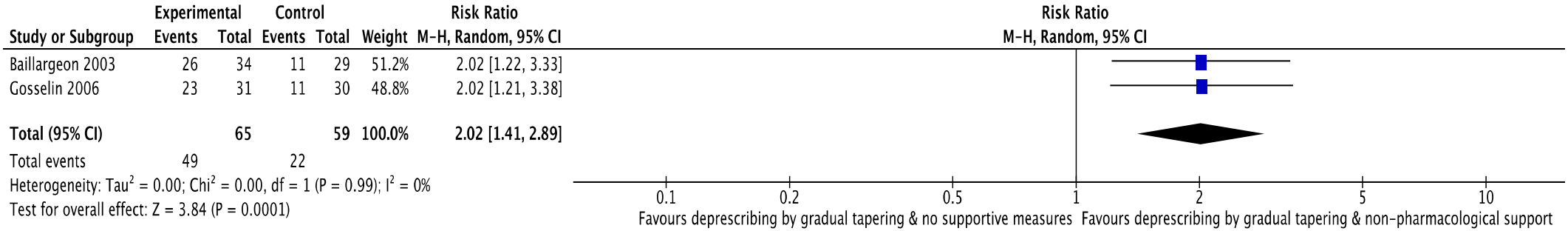

Figure 3 Forest plot of comparison 1. Deprescribing by GT alone versus deprescribing by GT and non-pharmacological support: dichotomous data, analysis method RR, outcome: 1.1a successful withdrawal from BZRA(s) over the short-term

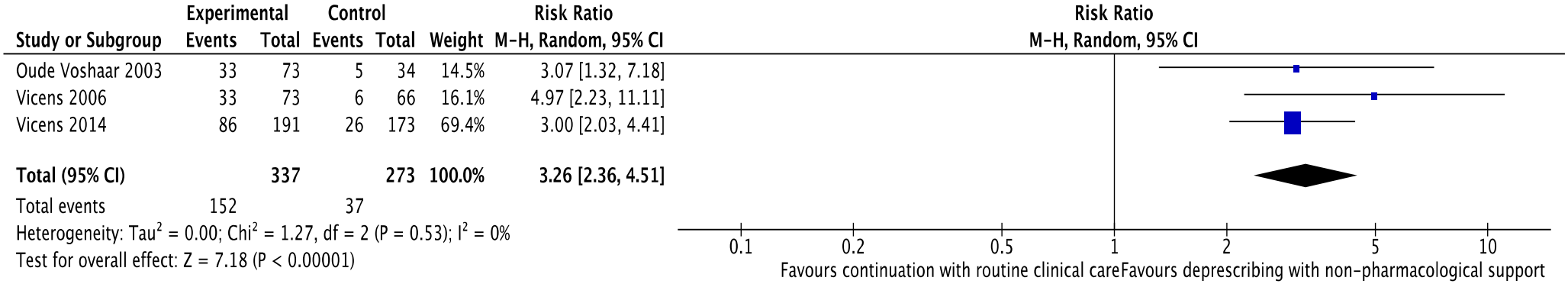

Figure 4 Forest plot of comparison 2. Continuation with routine clinical care versus deprescribing by GT and non-pharmacological support: dichotomous data, analysis method RR, outcome: 1.1b successful withdrawal from BZRA(s) over the long-term

Patient: Adults taking at least one long-term BZRA that is not clinically indicated or not wanted by the patient.

Setting: Community, primary or outpatient care

Intervention: Deprescribing BZRA by GT & clinically supportive measures as stated

Outcome	Relative effect* (95%CI)	Number of participants (studies)	Quality of the evidence (GRADE)†
1.1.a Successful withdrawal from BZRA(s) over the short-term	Intervention: With non-pharmacological support Comparison: Deprescribing BZRA by GT & without clinically supportive therapies		
	2.02 (1.41, 2.89)	124 (2)	+++O MODERATE[1]
	Intervention: With pharmacological support Comparison: Deprescribing BZRA by GT & without clinically supportive therapies		
	3.26 (2.36, 4.51)	257 (3)	++OO LOW[2]
1.1.b Successful withdrawal from BZRA(s) over the long-term	Intervention: With non-pharmacological support Comparison: Deprescribing BZRA by GT & without clinically supportive therapies		
	2.45 (1.56, 3.85)	123 (2)	+++O MODERATE[1]
	Intervention: With non-pharmacological support Comparison: Continuation of BZRA with routine clinical care		
	3.26 (2.36, 4.51)	610 (3)	+++O MODERATE[1]
	Intervention: With pharmacological support Comparison: Abrupt discontinuation of BZRA		

	0.52 (0.20, 1.32)	42 (1)	+OOO VERY LOW[3]
	Intervention: With pharmacological support Comparison: Deprescribing BZRA by GT & without clinically supportive therapies		
	0.96 (0.58, 1.60)	89 (1)	+++O MODERATE[4]

*The relative effect (risk ratio) is based on the probability of successful withdrawal occurring with the deprescribing intervention over the control.

† As per GRADE Working Group grades of evidence (see explanations)

1 Limitations in the design and implementation, suggesting a high risk of bias

2 Limitations in study design and implementation, and unexplained heterogeneity in the reported results

3 Precision of results limited to a single study.

4 Precision of results limited to a single study, unclear study power, and serious limitations in design and implementation suggesting high risk of bias.

Table 1: Summary of findings from the included studies for the primary outcome 1.1 'successful withdrawal from BZRA(s) over the short and long term', sub-categorised by the intervention and comparator type.