BMC Urology

Research article

Sildenafil (Viagra) for male erectile dysfunction: a meta-analysis of clinical trial reports

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Published: 22 May 2002

BMC Urology 2002, **2**:6

Received: 1 March 2002
Accepted: 22 May 2002

This article is available from: http://www.biomedcentral.com/1471-2490/2/6

Abstract

Background: Evaluation of company clinical trial reports could provide information for meta-analysis at the commercial introduction of a new technology.

Methods: Clinical trial reports of sildenafil for erectile dysfunction from September 1997 were used for meta-analysis of randomised trials (at least four weeks duration) and using fixed or dose optimisation regimens. The main outcome sought was an erection, sufficiently rigid for penetration, followed by successful intercourse, and conducted at home.

Results: Ten randomised controlled trials fulfilled the inclusion criteria (2123 men given sildenafil and 1131 placebo). NNT or NNH were calculated for important efficacy, adverse event and discontinuation outcomes. Dose optimisation led to at least 60% of attempts at sexual intercourse being successful in 49% of men, compared with 11% with placebo; the NNT was 2.7 (95% confidence interval 2.3 to 3.3). For global improvement in erections the NNT was 1.7 (1.6 to 1.9). Treatment-related adverse events occurred in 30% of men on dose optimised sildenafil compared with 11% on placebo; the NNH was 5.4 (4.3 to 7.3). All cause discontinuations were less frequent with sildenafil (10%) than with placebo (20%). Sildenafil dose optimisation gave efficacy equivalent to the highest fixed doses, and adverse events equivalent to the lowest fixed doses.

Conclusion: This review of clinical trial reports available at the time of licensing agreed with later reviews that had many more trials and patients. Making reports submitted for marketing approval available publicly would provide better information when it was most needed, and would improve evidence-based introduction of new technologies.

Background

Meta-analyses that include otherwise unpublished randomised trials are uncommon [1], but are welcome, and can inform in circumstances where information is contradictory. The example of tramadol in acute pain, where information on 3,500 patients was made available, explained the results of two studies, one showing that tramadol was a highly efficacious analgesic [2], the other showing it to be no different from placebo [3]. The truth was somewhere between. Despite the fact that tramadol had been in common use in some European countries for many years, fulfilling regulatory requirements for the

United States required studies to be conducted to contemporary requirements, and meta-analysis brought useful results to light.

Meta-analysis of randomised studies before a new technology has become commercially available is even more rare, though there is at least two examples [4,5]. Meta-analyses are usually performed some years after first commercial availability because the publication of randomised trials performed for efficacy and/or safety reasons takes time. The importance of meta-analysis in drug development and regulatory procedures is increasingly recognised [5,6].

The results of meta-analysis are undoubtedly important, both in the regulatory process and for evaluation of rare but serious adverse events. For COX-2 inhibitors meta-analysis was being planned before the randomised trials in order to examine the relationship between treatments and rare events [5,6].

The point of greatest change, though, is in the period immediately after commercial introduction. Media interest can raise patient expectations at a time where healthcare professionals and organisations have least knowledge and experience, and when few have had the opportunity to consider the full implications of the new technology on budgets and services. For sildenafil, for instance, 85% of first time prescriptions occurred in the first 12 weeks of availability in one New England healthcare provider [7]. It is at this point, the point of marketing approval, when there is the greatest need for the best information. At best only a small number of trials may have been published, and though they can be large, and usually are powered to detect a difference from placebo or common current practice, they are unlikely to be able to measure accurately the size of the benefit.

We sought to assess whether clinical trial reports presented for marketing approval would provide the basis for a systematic review at the time of launch if they were publicly available. We did this with reference to the erectile dysfunction treatment sildenafil (Viagra), using clinical trial reports made available by Pfizer Ltd.

Methods

No search strategy was required because this review was of material made available by Pfizer UK Ltd in the form of clinical trial reports used in a marketing authorisation application for sildenafil (Viagra) in September 1997. QUORUM guidelines were otherwise followed [7]. The prior intention was to use studies that were relevant to the use of sildenafil in clinical practice. This required the setting to be the home, not the clinic, use of sildenafil as required, rather than fixed dosing schedules (such as daily tablets), and studies of a minimum duration, which we set arbitrarily as four weeks.

Excluded were studies with laboratory measures of penile tumescence or rigidity with single doses of sildenafil, studies that only investigated erectile function in a clinic setting, studies that used fixed daily dosing rather than as required, and studies that were shorter than four weeks. Included were randomised trials that investigated sildenafil, with efficacy or safety data, were longer than four weeks, conducted in the home setting, and with doses in the licensed range of 25 mg to 100 mg as required, although lower and higher doses would be analysed if there were sufficient information. Clinical trials in men with erectile dysfunction caused specifically by single causes like spinal cord trauma or diabetes were not included because, taken with the other data, they would constitute clinical heterogeneity.

Each report was scored for quality using a three item, 1–5 score, quality scale [8]. Points were awarded to studies according to whether they were randomised and double blind and mentioned withdrawals or drop-outs from the study. An additional point was awarded if the method of randomisation or double blinding was described and was appropriate.

From each trial we extracted the number of patients treated per group, dosing regimen, study design, and the number of patients with efficacy and/or safety outcomes. The denominator was the number of patients randomised so that results were on an intention-to-treat basis. This analysis includes all randomised patients regardless of the completion of diaries, protocol concordance or missing data. Patients with missing or illegible diary data were assumed to have 0% intercourse success rate. In addition, this analysis included sexual intercourse attempts that were unsuccessful for reasons not attributable to sildenafil i.e. factors other than the erection being insufficiently hard or long-lasting. RAM extracted the data into tables, and these were then read and checked by other authors.

For the review, a prior definition of efficacy was a man with a consistent three-part outcome, consisting of an erection, sufficiently rigid for penetration, and followed by successful intercourse. Other efficacy outcomes of interest were the number of men with the highest two responses on the International Index of Erectile Function (IIEF) questions 3 and 4, and global evaluations of treatment efficacy by patients [9]. The number of grade 3 or 4 erections (at least hard enough for penetration) and successful erections were also noted.

Adverse events were also sought. These were the number of men with any treatment-related adverse event, the total

number of men discontinuing, those discontinuing through lack of efficacy or through adverse events, adverse events rated severe or serious, and information on particular adverse events.

Outcomes actually available and chosen were

Efficacy

• Number of men in whom the proportion of successful attempts at sexual intercourse was more than 60%

• Number of men in whom the proportion of successful attempts at sexual intercourse was more than 40%

• Number of men reporting that their erections had been improved on a global question (global A; "Has the treatment you have been taking over the past four weeks improved your erections?").

Erections

• The weighted mean number of weekly erections was calculated.

• The weighted mean success rate was calculated.

• The weighted mean weekly number of successful occasions where intercourse occurred was calculated from these numbers.

Adverse events

• Treatment-related adverse events

• Severe adverse events

• Serious adverse events

• Dyspepsia

• Headache

• Vasodilation (flushing)

Discontinuations

• All-cause discontinuations

• Discontinuations due to inefficacy

• Discontinuations due to adverse events

A prior intention was to analyse effectiveness and harm according to dose. Dosing could be fixed, or could be optimised where patients took an initial dose of 50 mg, and then move up to 100 mg or down to 25 mg on subsequent occasions depending on their individual judgement of the efficacy or adverse events caused by that dose.

There was no intention of pooling mean data because the results were not known to have a normal distribution [10], but rather to find dichotomous data. Relative benefit and relative risk estimates were calculated with 95% confidence intervals using a fixed effects model [11]. No pooling was done unless there were at least two studies or at least 200 men in the comparison. The number needed to treat (NNT) and number needed to harm (NNH), with confidence intervals, were calculated by the method of Cook and Sackett [12]. Confidence intervals (95%) for single samples were calculated for proportions [13]. Heterogeneity tests were not used as they have previously been shown to be unhelpful [13]. Clinical criteria for homogeneity was defined before analysis and examined graphically [14]. Publication bias was not assessed using funnel plots as these tests have been shown to be unhelpful [15,16], and publication bias was not an issue here.

Relative benefit or risk was considered to be statistically significant when the 95% confidence interval did not include 1. NNT or NNH values were only calculated when the relative risk or benefit was statistically significant, and are reported with the 95% confidence interval. Statistical significance of any difference between numbers needed to treat for different doses was assumed if there was no overlap of the confidence intervals, and additionally tested using the z statistic [16]. Calculations were performed using Microsoft Excel 98 on a Power Macintosh G4.

Results

Twenty-seven clinical trial reports were made available, all prepared for a marketing authorisation application, and dated September 1997. Some of these were single dose use in laboratory setting with penile plethysmography as an outcome. Others were open extensions of randomised studies. These were not useful, and 17 were excluded; details of excluded studies and reasons for exclusions are given in Additional File 1. There were no details of any ongoing studies.

Ten studies could be included (study report numbers 101, 102, 103, 106, 355, 356, 359, 361, 363, 364) with 1846 men given sildenafil (25 to 100 mg) and 1131 given placebo. An additional 277 men were given sildenafil at 5 mg or 200 mg. Details of trial design for the included studies is given in Additional File 2. Nine were parallel group and one had a crossover design, with fixed doses of sildenafil, or dose-optimised sildenafil, or both, and all had a placebo comparator group. Study duration was a minimum of six weeks and a maximum of six months.

Description of included studies

The number or percentage of men with various efficacy (more than 60% or 40% success, global rating, number erections and successful attempts at intercourse)(includ-

ing treatment related adverse events and discontinuations) and adverse event outcomes are shown for individual trials in Additional File 3. These outcomes were taken at 12 weeks, or at a time as close to 12 weeks as possible.

All ten of the included clinical trial reports had a quality score of 3 (two) or 4 (eight) out of 5. All were randomised but only two stated how randomisation was achieved. All stated that they were double blind, and six explained how blinding was achieved (double-dummy, identical placebo). All studies described withdrawals clearly and were performed on an intention-to-treat basis incorporating patients with unsuccessful attempts for reasons not associated with sildenafil.

For inclusion in a study a man typically had to have a minimum six-month history of erectile dysfunction, be 18 years or older, be in a heterosexual relationship for at least six months and be able to give written consent. There was typically a long (21 point) list of exclusions that included anatomical deformities, other sexual disorders, diabetes with poor control and/or untreated proliferative retinopathy, recent (six month) history of heart attack or stroke, significant cardiovascular disease, active peptic ulceration or bleeding, use of other treatments for erectile dysfunction and known history of retinitis pigmentosa. All of the clinical exclusions were sensible and would form part of clinical advice regarding advisability of any new treatment. Nine of the ten studies described men as having erectile dysfunction of organic, mixed and psychogenic aetiology; a small number of men in the trials also had diabetes.

Typically men would attend for a screening visit to record medical information and to have a physical examination. Treatments were to be taken as required before anticipated sexual activity on an outpatient basis over periods up to 12 weeks. No more than one treatment was to be taken on any one day.

Efficacy was determined using the 15 questions of the IIEF questionnaire, plus a global efficacy assessment ("Has the treatment you have been taking over the past four weeks improved your erections?"), plus a log or erectile function recording details of erections, their hardness, its duration, and whether or not erection was maintained long enough to complete the sexual activity. The main reported outcomes were responses to IIEF questions 3 ("Over the past four weeks, when you attempted sexual intercourse, how often were you able to penetrate your partner?") and question 4 ("Over the past four weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?").

Adverse events, observed or volunteered, were recorded, and investigators were to pursue all adverse events. Serious adverse events were defined as fatal, life-threatening, permanently disabling, requiring hospital admission, congenital abnormality, cancer or overdose, or considered serious enough for immediate reporting.

Results Of meta-analysis

Efficacy

The efficacy results closest to the prior definition of efficacy of a man with the consistent three part outcome, consisting of an erection, sufficiently rigid for penetration, and followed by successful intercourse were the number of men in whom at least 60% or at least 40% of attempts at sexual intercourse were successful. The results for at least 60% of attempts successful are shown in Table 1 and Figure 1. All doses were significantly better than placebo. In three studies 48% of men had this outcome with dose optimisation compared with 11% with placebo; the number needed to treat was 2.7 (95% CI 2.3 to 3.2). Dose-optimisation produced a significantly lower (better) NNT than a 25 mg fixed dose.

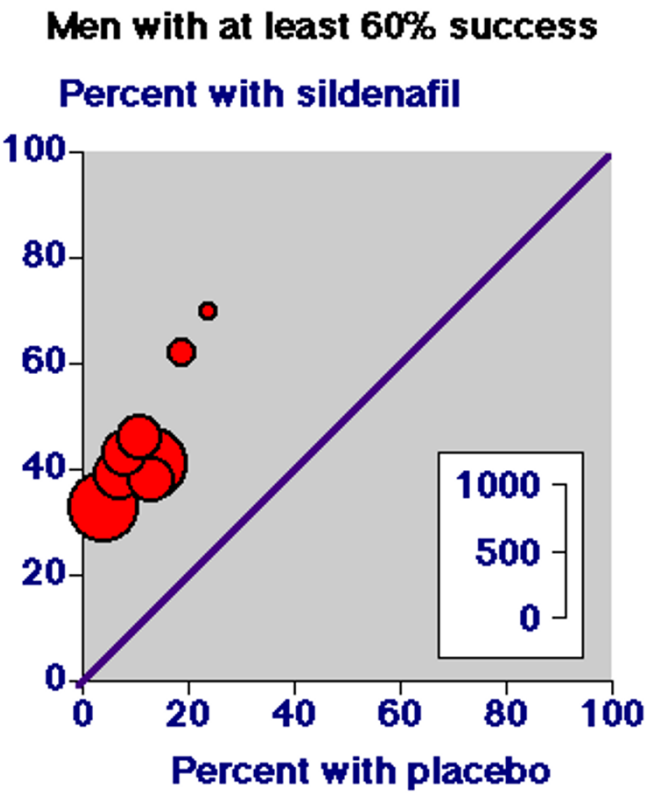


Figure 1
Each symbol represents the percentage of men with at least 60% success with viagra or placebo. Size of the symbol is proportional to the size of the study

Table 1: At least 60% of attempts at sexual intercourse successful

		Number (%) with outcome			
Dosing (mg)	**Number of trials**	**Sildenafil**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**
25	3	88/312 (28)	43/426 (10)	3.0 (2.1 to 4.2)	5.5 (4.2 to 8.1)
50	5	216/511 (42)	62/607 (10)	4.3 (3.3 to 5.6)	3.1 (2.7 to 3.7)
100	5	223/506 (44)	62/607 (10)	4.4 (3.4 to 5.8)	3.0 (2.6 to 3.5)
200	2	93/191 (49)	19/181 (10)	4.5 (2.9 to 7.1)	2.6 (2.2 to 3.4)
Dose optimised	3	183/379 (48)	43/376 (11)	4.2 (3.1 to 5.6)	2.7 (2.3 to 3.2)

Table 2: At least 40% of attempts at sexual intercourse successful

		Number (%) with outcome			
Dosing (mg)	**Number of trials**	**Sildenafil**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**
25	3	122/312 (39)	70/426 (16)	2.6 (2.0 to 3.3)	4.4 (3.4 to 6.2)
50	5	269/511 (53)	102/607 (17)	3.3 (2.7 to 4.0)	2.8 (2.4 to 3.3)
100	5	272/506 (54)	102/607 (17)	3.3 (2.7 to 4.1)	2.7 (2.4 to 3.2)
200	2	106/191 (55)	32/181 (18)	3.1 (2.2 to 4.3)	2.6 (2.1 to 3.5)
Dose optimised	3	227/379 (60)	70/376 (19)	3.2 (2.6 to 4.0)	2.4 (2.1 to 2.9)

The results for at least 40% success are shown in Table 2 and Figure 2. All doses were significantly better than placebo. In three studies 60% of men had this outcome with dose optimisation compared with 19% with placebo; the number needed to treat was 2.4 (95% CI 2.1 to 2.9). Dose-optimisation produced a significantly lower (better) NNT than a 25 mg fixed dose.

More men responded positively to the global question about improved erections with sildenafil than with placebo (Table 3, Figure 3). All doses were significantly better than placebo. In five studies 79% of men responded positively with dose optimisation compared with 21% with placebo; the number needed to treat was 1.7 (1.6 to 1.9). Dose-optimisation produced a significantly lower (better) NNT than 25 mg and 50 mg fixed doses.

Responses on IIEF questions 3 and 4 were not given as proportions, but as means. Pooling of mean data was not attempted.

Erections

The weighted mean number of erections per week and successful erections in which intercourse took place with different doses of sildenafil and with placebo are shown in Figure 4. With placebo erections with successful intercourse occurred on average less often than once every five weeks. With dose optimised sildenafil they occurred more often than once a week. Dose optimisation produced more successful erections, and more erections in total, than did 50 mg or 100 mg fixed dose sildenafil.

Adverse events

Treatment related adverse events are shown in Table 4. They occurred more frequently with sildenafil than with placebo for all doses. Dose optimisation produced 30% of patients with adverse events compared with 11% with placebo; the number needed to harm was 5.4 (4.3 to 7.3). This was significantly greater (better) than 100 mg and 200 mg fixed doses.

Serious adverse events were no more frequent with sildenafil than placebo at any dose (Additional File 4). Adverse

Table 3: Positive response to global question about improved erections

Dosing (mg)	Number of trials	Number (%) with outcome			NNT (95% CI)
		Sildenafil	Placebo	Relative benefit (95% CI)	
25	3	192/312 (62)	114/426 (27)	2.3 (1.9 to 2.8)	2.8 (2.4 to 3.5)
50	5	378/511 (74)	153/607 (25)	3.0 (2.6 to 3.5)	2.1 (1.9 to 2.3)
100	5	415/506 (82)	153/607 (25)	3.3 (2.9 to 3.8)	1.8 (1.6 to 1.9)
200	2	152/191 (80)	39/181 (22)	3.7 (2.8 to 5.0)	1.7 (1.5 to 2.0)
Dose optimised	5	411/517 (79)	111/524 (21)	3.8 (3.2 to 4.5)	1.7 (1.6 to 1.9)

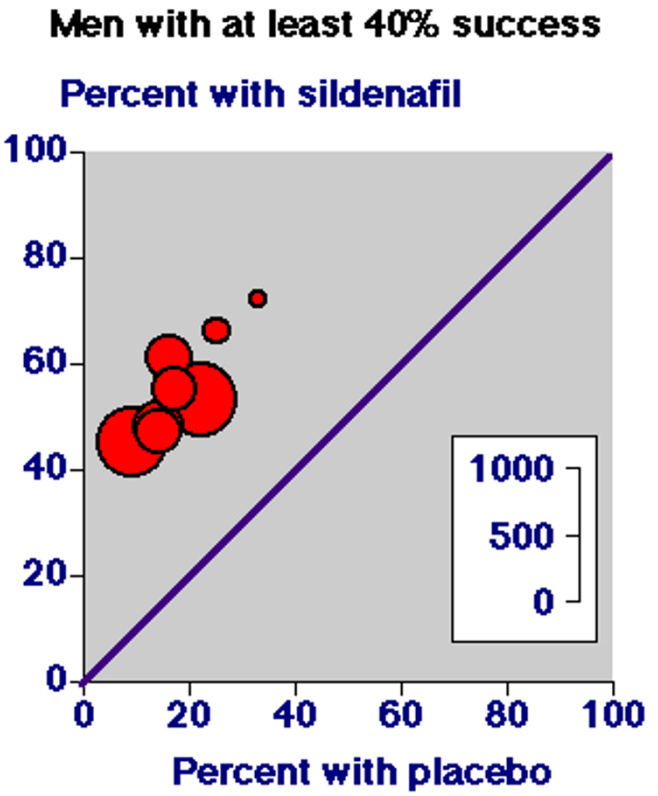


Figure 2
Each symbol represents the percentage of men with at least 40% success with viagra or placebo. Size of the symbol is proportional to the size of the study

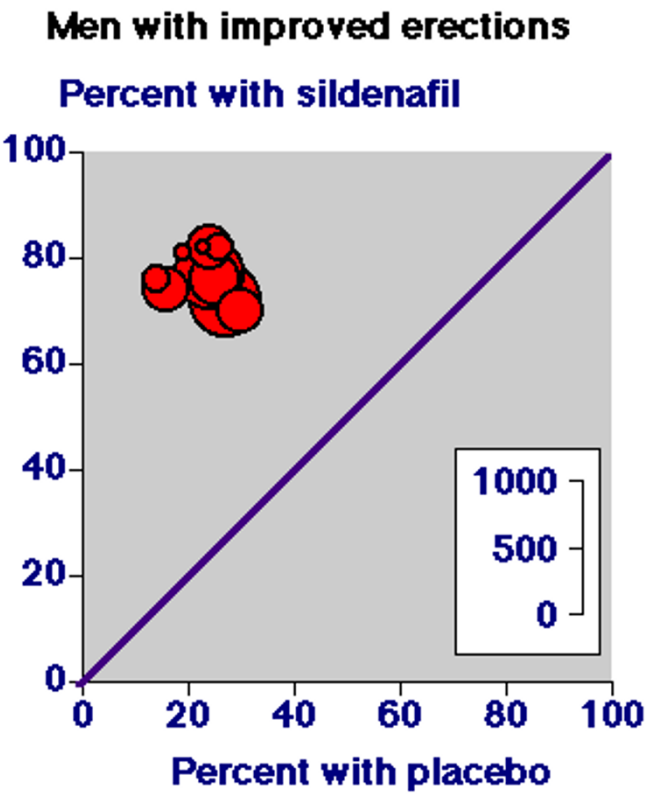


Figure 3
Each symbol represents the percentage of men with improved erections with viagra or placebo using the global score. Size of the symbol is proportional to the size of the study

events described as severe occurred more frequently than placebo with 100 mg and 200 mg fixed doses, but not with dose optimisation or 25 mg or 50 mg fixed doses (Additional File 5).

Consistent information was available from clinical trial reports for three specific adverse events – dyspepsia, headache and vasodilation. The incidence of these all increased with dose (Table 5), resulting in lower (worse) values for NNH. For dyspepsia, dose optimisation produced signifi-

Table 4: Treatment related adverse events

Dosing (mg)	Number of trials	Number (%) with outcome		Relative risk (95% CI)	NNH (95% CI)
		Sildenafil	Placebo		
25	3	71/312 (23)	33/426 (8)	2.8 (1.9 to 4.2)	6.7 (4.9 to 10)
50	5	190/508 (37)	59/607 (10)	3.7 (2.8 to 4.8)	3.6 (3.1 to 4.4)
100	5	260/506 (51)	59/607 (10)	5.0 (3.9 to 6.5)	2.4 (2.2 to 2.7)
200	2	137/191 (72)	26/181 (14)	5.0 (3.5 to 7.2)	1.7 (1.5 to 2.0)
Dose optimised	5	155/517 (30)	60/524 (11)	2.6 (2.0 to 3.4)	5.4 (4.3 to 7.3)

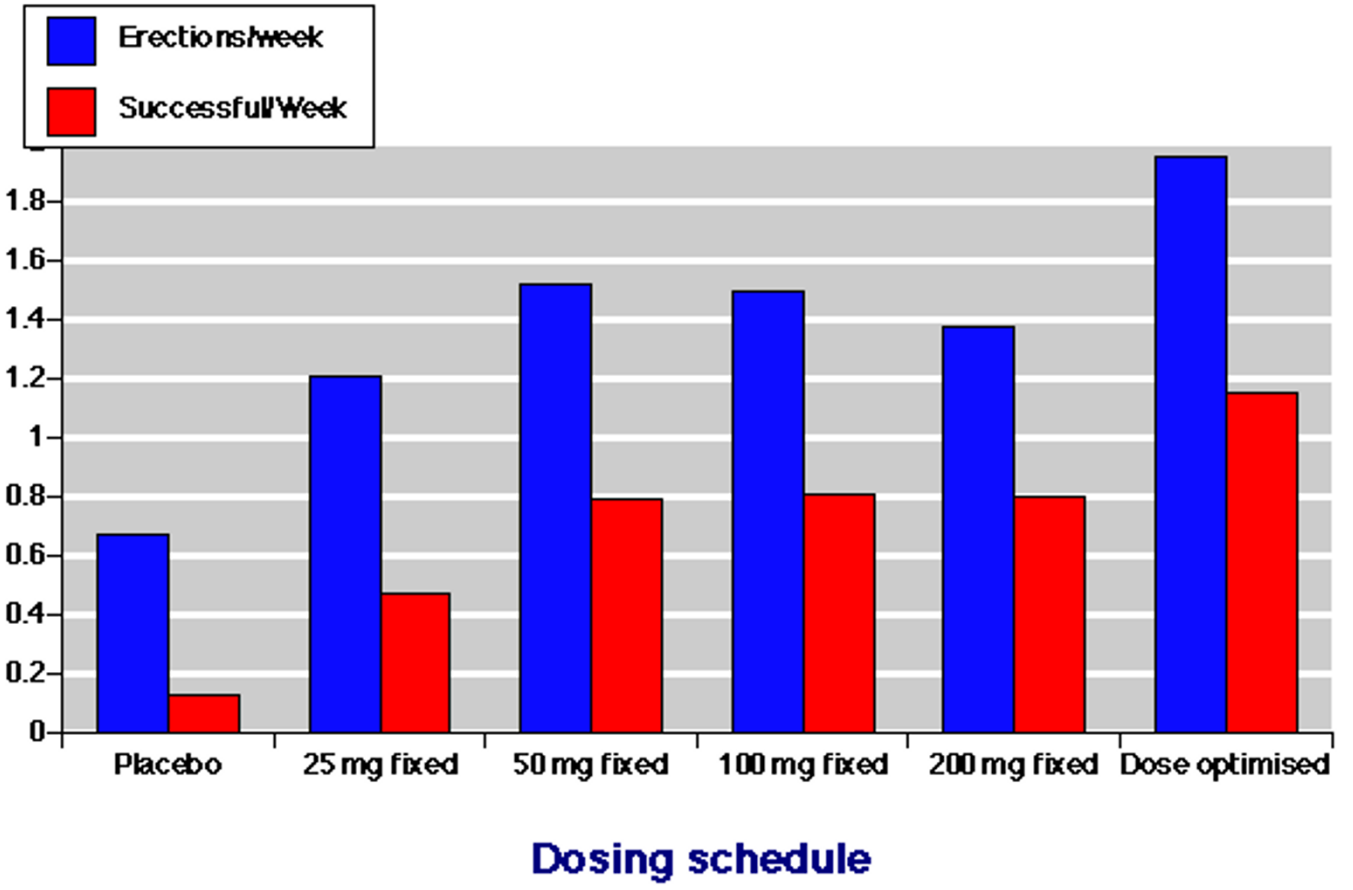


Figure 4
Mean number of erections a week (blue), and erections resulting in successful intercourse (red) with placebo and different doses and dosing schedules of sildenafil

cantly higher (better) NNH values than did 50 mg, 100 mg or 200 mg. For headache, dose optimisation produced significantly higher NNH values than 100 mg and 200 mg. For vasodilation, dose optimisation produced similar NNH values to all fixed doses.

Discontinuations

All cause discontinuations are shown in Table 6. All cause discontinuations were significantly lower with sildenafil at 50 mg and 100 mg fixed doses and with dose optimisation.

Table 5: Specific adverse events (treatment related) in comparisons with placebo

			Number (%) with outcome			
Dosing (mg)	**Number of trials**	**Adverse event**	**Sildenafil**	**Placebo**	**Relative risk (95% CI)**	**NNH (95% CI)**
25	3	Dyspepsia	4/312 (1.2)	1/426 (0.2)	4.4 (0.6 to 34)	
		Headache	31/312 (10)	14/426 (3.2)	3.1 (1.6 to 6.1)	15 (9.6 to 34)
		Vasodilation	30/312 (9.6)	4/426 (1.0)	11 (3.8 to 29)	12 (8.3 to 19)
50	5	Dyspepsia	24/511 (4.7)	4/607 (0.7)	6.4 (2.4 to 17)	24 (17 to 47)
		Headache	77/511 (15)	21/607 (0.3)	4.5 (2.8 to 7.3)	8.6 (6.6 to 12)
		Vasodilation	94/511 (18)	11/607 (1.8)	9.7 (5.4 to 18)	6.0 (5.0 to 7.7)
100	5	Dyspepsia	60/506 (12)	4/607 (0.7)	15 (5.8 to 40)	8.9 (7.1 to 12)
		Headache	115/506 (23)	21/607 (0.3)	6.8 (4.3 to 11)	5.2 (4.3 to 6.5)
		Vasodilation	90/506 (17)	11/607 (1.8)	9.2 (5.0 to 17)	6.3 (5.1 to 8.0)
200	2	Dyspepsia	35/191 (18)	3/181 (1.7)	11 (3.5 to 35)	6.0 (4.5 to 9.2)
		Headache	62/191 (32)	7/181 (3.9)	8.4 (4.0 to 18)	3.5 (2.8 to 4.7)
		Vasodilation	43/191 (22)	7/181 (3.9)	5.9 (2.7 to 13)	5.4 (4.0 to 8.3)
Dose optimised	5	Dyspepsia	24/517 (4.6)	7/524 (1.3)	3.4 (1.5 to 7.9)	31 (19 to 82)
		Headache	63/517 (12)	10/524 (1.9)	6.3 (3.2 to 12)	9.8 (7.5 to 14)
		Vasodilation	65/517 (13)	4/524 (0.8)	16 (6.0 to 44)	8.5 (6.7 to 11)

Table 6: All cause discontinuations

		Number (%) with outcome			
Dosing (mg)	**Number of trials**	**Sildenafil**	**Placebo**	**Relative risk (95% CI)**	**NNH (95% CI)**
25	3	32/312 (10)	63/426 (15)	0.75 (0.50 to 1.11)	
50	5	36/508 (7)	86/607 (14)	0.52 (0.36 to 0.76)	-14 (-9 to -28)
100	5	47/506 (9)	86/607 (14)	0.67 (0.47 to 0.95)	-20 (-12 to -89)
200	2	18/191 (9)	23/181 (13)	0.76 (0.43 to 1.35)	
Dose optimised	5	52/517 (10)	104/524 (20)	0.50 (0.37 to 0.67)	-10 (-7 to -18)

Discontinuations because of lack of efficacy were significantly lower with sildenafil at 50 mg and 100 mg fixed doses and with dose optimisation (Additional File 6).

Discontinuations due to adverse effects were not different between sildenafil at any dose and placebo (Additional File 7).

Discussion

This review demonstrated that considerable amounts of useful information are available in clinical trial reports submitted for marketing authorisation (licensing). That information adequately describes research methods used, though could be improved, perhaps using the updated CONSORT criteria [17]. If these guidelines are becoming necessary for publication of randomised trials in our major medical journals, then they should be minimum criteria for clinical trials reports required by licensing authorities. We did not check the reports against each CONSORT criterion because the reports were from 1997 soon after the publication of the original CONSORT statement [17].

Despite scores of 3 or 4 out of five on a commonly-used quality score, and acknowledging that scores like this are not associated with bias [18,19], the areas where the clin-

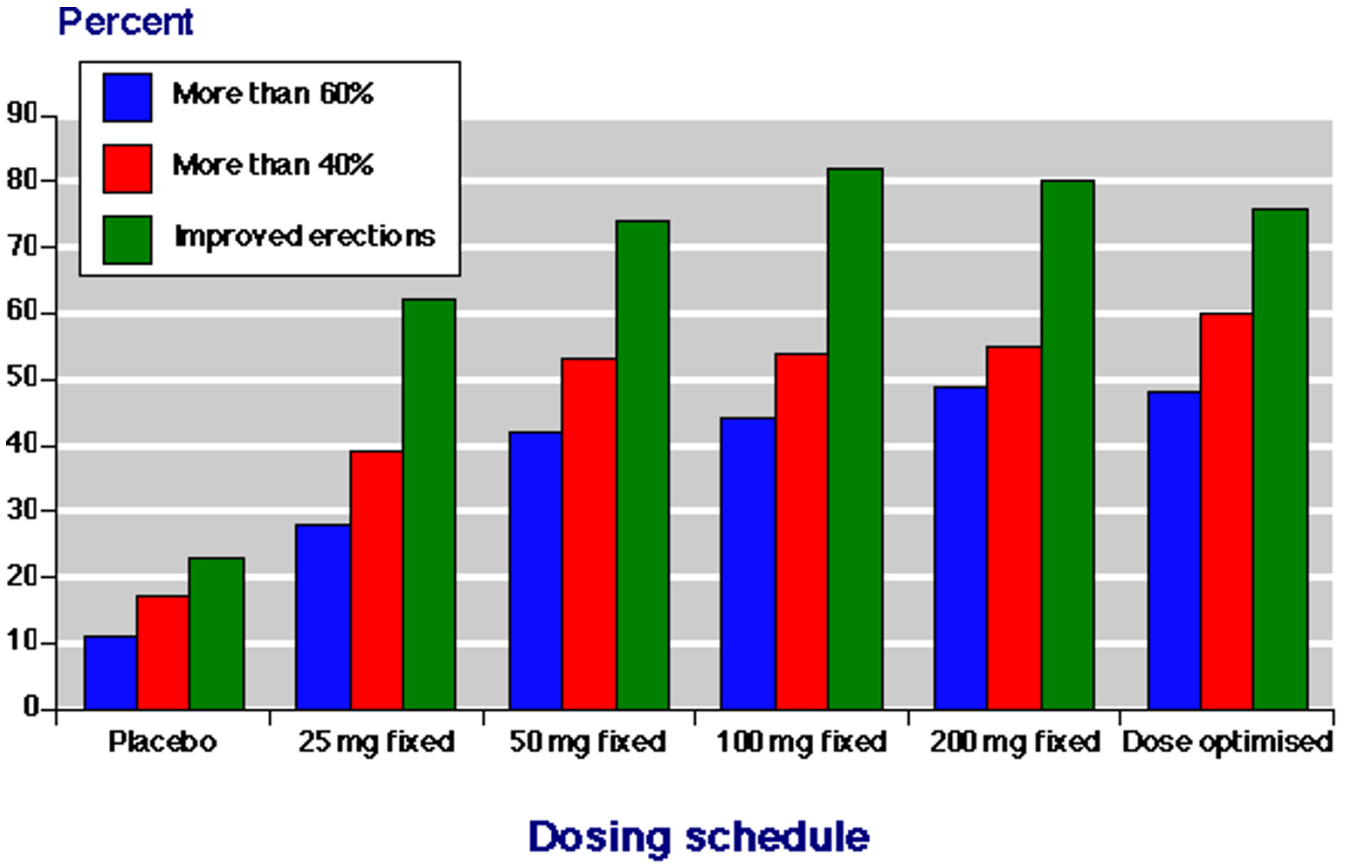


Figure 5
Mean percentage of men achieving the outcomes of more than 60% success (blue) more than 40% success (red) and improved erections on the global question (green) with placebo and different doses and dosing schedules of sildenafil

ical trials reports were weak were important ones. Only two reports stated how the randomisation sequence was generated. No report adequately described allocation concealment, though several mentioned sealed envelopes. No report described the implementation of the allocation sequence. Only two reports described how double blinding was achieved.

In other areas, reporting was good. Participants, and inclusion and exclusion criteria were explicit, as was a description of the intervention. Patient flow (though without diagrams) was thoroughly described, together with reasons for withdrawal. Baseline information on participants, numbers analysed and methods used were all well described, both for efficacy and adverse events. One criticism, outside CONSORT, was the use of mean scores for results of IIEF questions. Mean scores are of little value, especially when there may not be a normal distribution when they can be misleading [10]. Better would be the number or proportion of men achieving good or excellent outcomes.

Clinical trial reports were a good source of information, and with minor changes would become an excellent source of information for meta-analysis. For sildenafil in erectile dysfunction these reports allowed interesting conclusions to be drawn from a homogeneous population of men with similar aetiologies, but excluding those with erectile dysfunction following spinal cord trauma, with diabetes, or following treatment for prostate cancer. Although two small studies on spinal cord trauma and one on diabetes were available in the full review, much more information on men with erectile dysfunction of particular aetiology has become available since 1997 [19], [19], [20], [21], [22], [23].

Efficacy was available in a number of formats in addition to mean responses to IIEF scores 3 and 4. The number of men in whom sildenafil was successful (erections hard enough for penetration, and resulting in intercourse) more than 60% of the time, and more than 40% of the time was available, and chosen by us for evaluation. Cut points every 20% from 0% to 100% were also available.

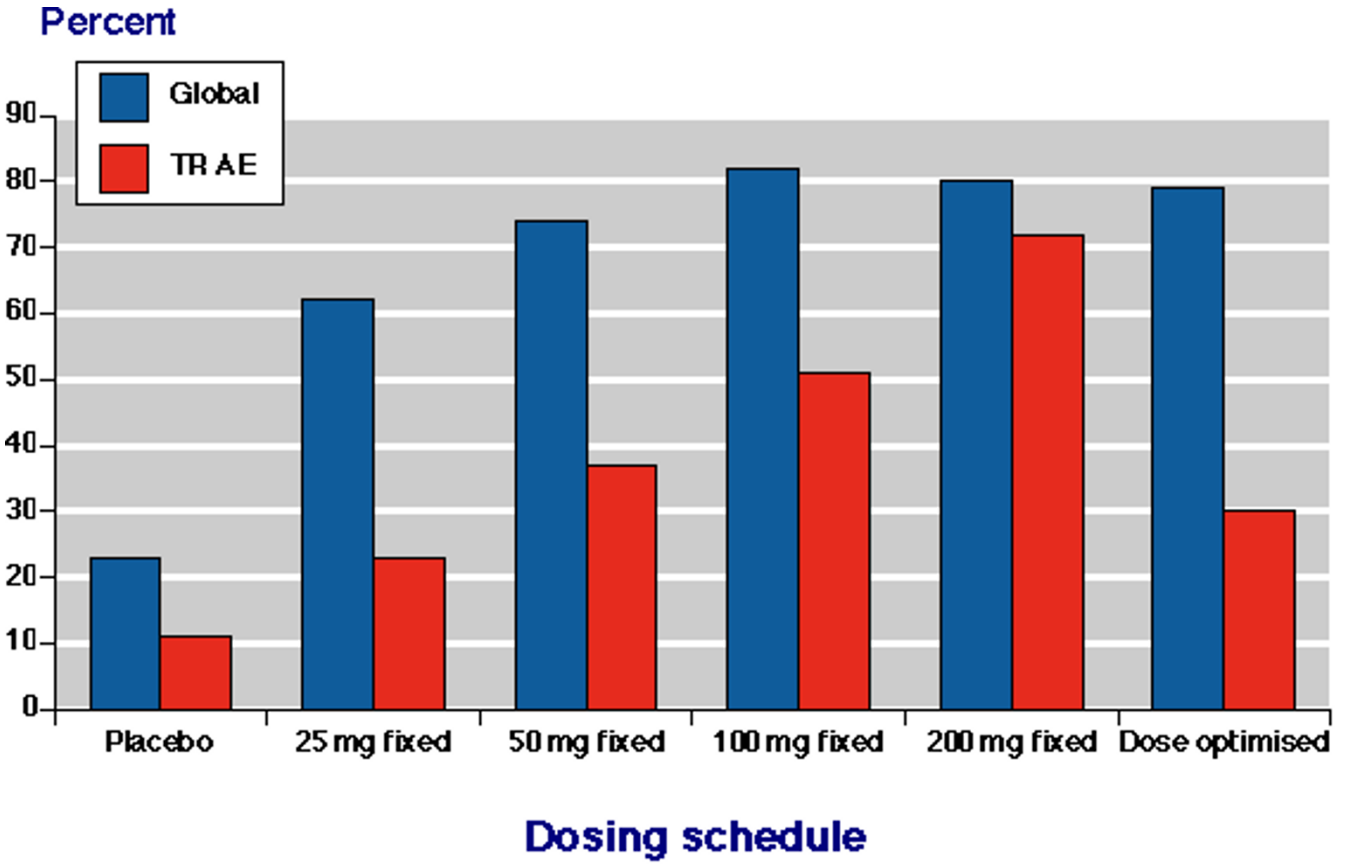


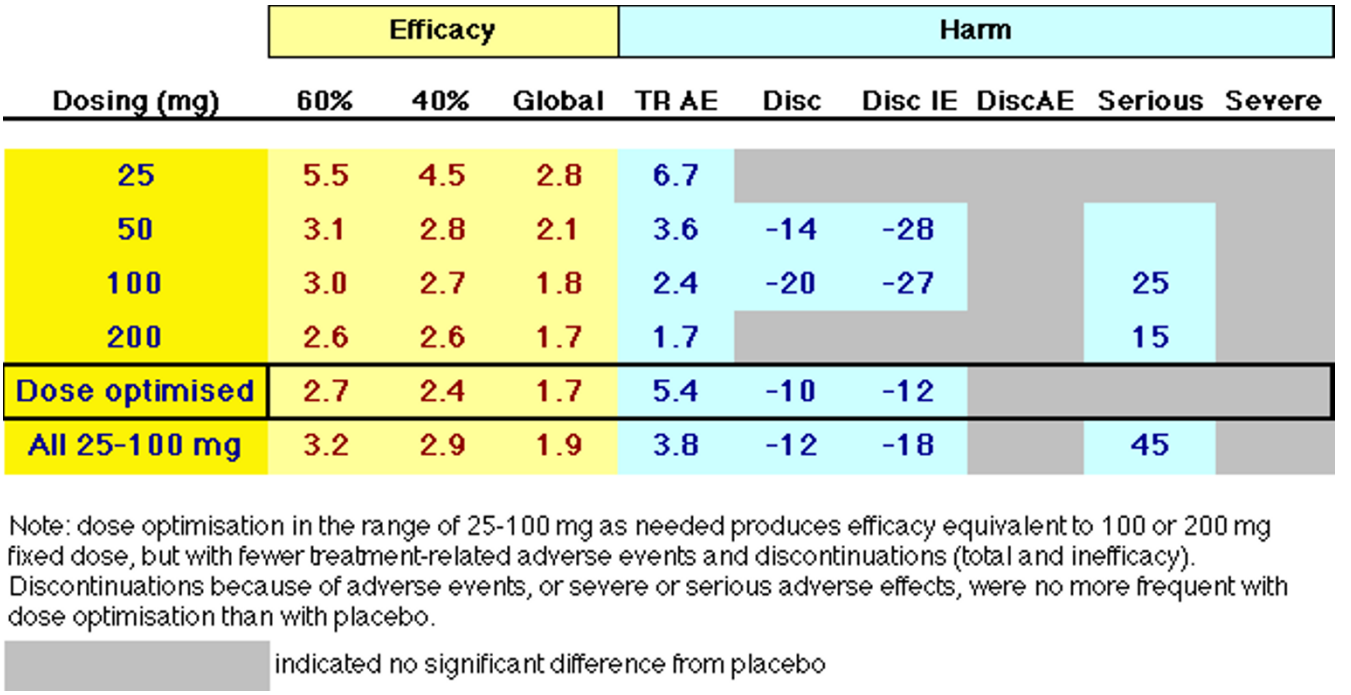
Figure 6
Mean percentage of men with improved erections on a global scale (blue), and reporting treatment related adverse effects (red) with placebo and different doses and dosing schedules of sildenafil

The number of men responding positively to the global question on improved erections was also available. Clearly there is a gradation here from outcomes that are less easy to achieve to those that are easier to fulfil. A greater proportion of men achieved the easier than harder outcome for all doses (Figure 5). Numbers needed to treat and the proportion of patients achieving the outcome could easily be calculated.

Adverse events were also well described, and presented in a number of formats, from the number of men with any treatment related adverse event, through the number with severe or serious adverse events, particular adverse events, and discontinuations. From these it was possible to calculate numbers needed to harm and the proportion of patients for each outcome.

The ability to perform these calculations with information pooled from 10 studies was informative. Firstly, it supported the optimised dosing regimen for sildenafil. Optimised dosing produced efficacy equivalent to the highest fixed dose, and harm equivalent to the lowest fixed dose. Figure 6 shows the effects on the two broadest efficacy and harm outcomes, global response about improved erections and treatment related adverse effects. Figure 7 shows the NNTs and NNHs for three efficacy outcomes, three harm outcomes and three discontinuation outcomes. Optimised dosing was better than fixed dosing.

It is also germane to enquire whether results obtained from clinical trial reports of the earliest studies are borne out in later reviews. A review of 20 trials comparing sildenafil with placebo with about 4,000 men included both published and unpublished information, and supplemented by the manufacturer where appropriate, arrived at broadly similar results [24]. Only seven of the references to trials in that review were dated 1997 or before (mostly as abstracts), and would have been available at the time of marketing approval. Though combining all doses of sildenafil from 5 mg to 200 mg and dose escalation together in a comparison with placebo, the result for global efficacy



	Efficacy			Harm					
Dosing (mg)	60%	40%	Global	TR AE	Disc	Disc IE	DiscAE	Serious	Severe
25	5.5	4.5	2.8	6.7					
50	3.1	2.8	2.1	3.6	-14	-28			
100	3.0	2.7	1.8	2.4	-20	-27		25	
200	2.6	2.6	1.7	1.7				15	
Dose optimised	2.7	2.4	1.7	5.4	-10	-12			
All 25-100 mg	3.2	2.9	1.9	3.8	-12	-18		45	

Figure 7
Number needed to treat for different efficacy outcomes (more than 60% success, more than 40% success and improvement on global question) and number needed to harm for different adverse event outcomes (treatment related adverse events, all cause discontinuations, discontinuations due to inefficacy and adverse events and serious and severe adverse events). For NNT low numbers are better and for NNH high or negative numbers are better. TR AE – treatment related adverse event, Disc – discontinuation

yielded an NNT of 2, the same as is found in this review for all doses higher than 25 mg (Table 3).

This investigation of the evidential properties of clinical trial reports of sildenafil for treatment of erectile dysfunction indicates that, in this instance, reports could have been used for systematic review at the time of product launch. With little additional effort the clinical trial reports could have fulfilled CONSORT guidelines for the reporting of randomised controlled trials. Making clinical trial reports publicly available at the time of product launch, perhaps through the Internet, would make their introduction evidence-based, as well as allowing healthcare services to plan ahead more effectively. This would benefit commercial organisations by maximising the uptake of effective new technology, and may accelerate discontinuation of less effective, or less safe, older technology.

Conclusions

Clinical trial reports presented for marketing approval did provide the basis for a systematic review at the time of launch for sildenafil for the treatment of male erectile dysfunction. To our knowledge these documents were not publicly available at the time. Were clinical trials reports used for marketing approval publicly available, then review and meta-analysis would allow an early appreciation of benefits or pitfalls§for patients and healthcare systems.

Competing interests

RAM has received lecture fees on one occasion related to erectile dysfunction. All authors have worked with commercial, government and charities in relation to healthcare, but not in regard to erectile dysfunction.

Authors' contributions

RAM read each report, abstracted information and analysis, and performed quality scoring. JE read each report, checked abstracted information and analysis, and performed quality score. HJM checked quality scores. All authors contributed equally to the preparation and writing of the manuscript.

Additional material

Additional file 1

Excluded studies – a list of the studies excluded from the review.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S1.pdf]

Additional file 2

Included studies – a list of the studies included with details of patient condition, design, dosing, controls, blinding, entry criteria and quality score.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S2.pdf]

Additional file 3

Details of the results for included studies for each treatment group in each study. Efficacy variables (erections and sexual intercourse) and adverse events (including discontinuations) are listed.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S3.pdf]

Additional file 4

Details of serious adverse results by dose.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S4.pdf]

Additional file 5

Details of severe adverse results by dose.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S5.pdf]

Additional file 6

Details of inefficacy discontinuations by dose.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S6.pdf]

Additional file 7

Details of adverse event discontinuations by dose.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2490-2-6-S7.pdf]

Acknowledgements

The work was supported by an unrestricted educational grant from Pfizer Ltd, and by Pain Research Funds. The terms of the Pfizer grant included an absolute right of the authors to publish the results of their work. Pfizer did see the manuscript before submission.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2490/2/6/prepub