

The Leeds Sleep Evaluation Questionnaire in Psychopharmacological Investigations — a Review

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Abstract. The Leeds Sleep Evaluation Questionnaire comprises ten self-rating 100-mm-line analogue questions concerned with aspects of sleep and early morning behaviour. The questionnaire has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigations involving a variety of psychoactive agents, including sedative-hypnotics, antidepressants, anxiolytics, CNS stimulants, and antihistamines.

Dose-related improvements in the self-reported ratings of getting to sleep and perceived quality of sleep were generally associated with reductions in the self-reported levels of alertness and behavioural integrity the morning following the nocturnal administration of sedative hypnotic and anti-anxiety agents. Psychostimulants, on the other hand, impaired subjective ratings of sleep and produced increases in early morning assessments of alertness. Certain antidepressant and antihistaminic agents produced effects similar to the sedative-hypnotics, while others did not affect self-reported aspects of sleep and early morning behaviour.

Key words: Analogue rating scales — Benzodiazepines — Hypnotics — Sleep

Johns (1971) in a comparative review of the different methods for assessing sleep, suggested that subjective, self-reports were sensitive to changes in sleep, especially in psychopharmacological investigations. Samuels (1964) demonstrated the empirical usefulness of self-ratings in an investigation of sleep in hospitalized depressed patients. He showed that patient's own ratings of sleep discriminated significantly between drug and placebo nights, but that nurses' ratings of the patients' sleep did not make a significant discrimi-

nation. Lewis (1969) compared subjective estimates of sleep with objective EEG evaluations, and although subjects tended to overestimate the delay in getting to sleep and underestimate the total sleep time, the objective measures and subjective self-evaluations did correlate. Adam et al. (1976) also demonstrated a close correspondence between self-reported changes and EEG changes related to drug administration.

One of the most frequently employed measures for self-assessment of sleep is the 100-mm-line visual analogue self-rating scale (Aitken 1969; Lader and Norris 1969; Herbert et al. 1976). Visual analogue scales consist of a 100-mm-horizontal line with two extreme states defined at the ends of the line (e.g. alert/not-alert). The subject responds by placing a vertical mark on the line to indicate his present self-evaluation. Although the questions used vary between researchers, there is a degree of communality. There is generally a question concerning sleep onset (very abrupt — very slow, Bond and Lader 1975; I fell asleep never — immediately, Adam et al. 1976); and a question concerning the quality of sleep, (a very good night's sleep — a very bad night's sleep, Salkind and Silverstone 1975; I slept very badly — very well, Nicholson et al. 1976). Behavioural aspects of awakening, and general feelings of vitality and alertness in the period after awakening are also often rated, (Lader and Norris 1969; Adam et al. 1976). Dream content and quality (Firth 1974), and mood/feeling states in the morning (Lader and Norris 1969; Herbert et al. 1976), have also been measured.

The Leeds Sleep Evaluation Questionnaire (SEQ) contains ten questions pertaining to four consecutive aspects of sleep: getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS), and behaviour following wakefulness (BFW). The Leeds SEQ contains more questions than those generally used by other workers, where between three (Bond and Lader 1975), and five (Nicholson et al. 1976) questions are generally

Table 1. Summary table of investigations

Reference	Ref. no. (Tables 2-4)	Drug conditions and doses (mg/dose)	Dose regimen N = night M = morning TDS = 3/day	No. of subjects/ group	Placebo/ active comparison (see text)
Hindmarch (1975)	1	Temazepam 15, 20, 30 nitrazepam 5 amylobarbitone 100	N	20	B
Hindmarch (1976)	2	Temazepam 10, 20, 30	N	10	A
Hindmarch and Parrott (1977)	3	Nomifensine 25 imipramine 25	TDS	9	A
Hindmarch and Parrott (1978a)	4	Chlorpheniramine, mebhydrolin, clemastine ketotifen, promethazine	Various	10	A
Hindmarch and Parrott (1978b)	5	Clobazam, 20, 30, 40	N	10	A
Hindmarch and Parrott (1979)	6	Clobazam, 30 dipotassium chlorazepate 15	N	12	B
Hindmarch and Parrott (in press)	7	Dichloralphenazone and benzodiazepine combinations: acute	N	10	B
Hindmarch and Parrott (in press)	8	Dichloralphenazone and benzodiazepine combinations: repeated	N	12	A
Hindmarch and Parrott (unpublished)	9	Flurazepam 15	N	18	B
Hindmarch et al. (1977)	10	Dichloralphenazone 1,300 flunitrazepam 1 amylobarbitone 100	N	7	A
Hindmarch et al. (in press 1980)	11	Temazepam 40, 60	N	10	A
Hindmarch et al. (1980)	12	Nomifensine 25 nomifensine and clobazam amytriptiline and chlordiazepoxide combinations	TDS	16	B
Parrott et al. (in press 1980)	13a	Amphetamine sulphate 10	M	12	B
	13b	Amphetamine sulphate 10	M	10	B

presented. However the general area covered by these different questionnaires is very similar.

The present review is concerned with the Leeds SEQ results from a variety of psychopharmacological studies involving normal volunteer subjects. In most studies the Leeds SEQ was used to investigate a potential hypnotic agent, in comparison both to a placebo condition and to an active internal control (Hindmarch 1975; Hindmarch et al. 1977). In other studies the Leeds SEQ was used to monitor possible effects upon sleep associated with the administration of antihistamine or antidepressant agents (Hindmarch and Parrott 1977, 1978a).

Maxwell (1978) in a critical review of visual analogue self-rating scales has stated: "Overall clinical evaluation is always strengthened by consistency in results, consistency between different methods of measurement, and consistency between the results of different studies." The present review will allow con-

sistency of results to be gauged by comparing results from identical drug conditions in different studies. Dose-response relationships are also reported for sedative-hypnotics, again allowing the meaningfulness of the Leeds SEQ findings to be judged. Leeds SEQ ratings are also compared to analogue scale findings reported by other sleep researchers. Mention will also be made of the relationships between sleep questionnaire findings, and other indexes of sleep (e.g. EEG, sleep motility) which have been reported from other laboratories.

Materials and Methods

Experimental Design. In all reported investigations, active drug conditions were compared to placebo. Active-drug and placebo conditions were in identical matching capsules in all studies except Hindmarch and Parrott (1978a), where a variety of randomly assorted placebo and active-drug regimens were present. In all investigations, testing was double-blind. Two methods of comparing placebo and

Table 2. Sleep evaluation questionnaire values after single nocturnal doses of various sedative-hypnotic drugs compared to placebo baselines

Drug condition	Dose (mg)	Getting to sleep (GTS)	Quality of sleep (QOS)	Awakening from sleep (AFS)	Behaviour following wakefulness (BFW)	Reference no. (Table 1)
Amylobarbitone sodium	100	+ 4.2	+ 8.3	- 4.8	- 5.0	1
	100 ^a	+ 6.3*	+ 7.9	-19.6***	-12.8*	10
	100	+ 9.0*	+15.6	-10.4*	- 5.6*	8
Dichloralphenazone	325	+ 2.4	- 0.1	- 1.4	- 0.7	7
	650	+ 3.9	0.0	+ 2.3	+ 0.7	7
	1,300 ^a	+10.8***	+ 0.4	- 6.1	- 5.0	10
Nitrazepam	2.5	+ 2.5	+ 1.6	- 0.9	0.0	7
	5	+ 8.9*	+ 9.7*	- 6.1	-10.9**	1
	5	+ 6.2*	+ 4.5	- 2.0	- 3.6	7
	5	+ 6.6	+12.1*	-12.6**	- 5.8*	8
Clobazam	10	+ 0.4	+12.9**	- 4.2	- 2.3	7
	20	+ 2.1	+ 6.4	- 6.2	- 2.4	8
	30	+10.8**	+ 3.7	-13.0	-11.1	5
	40	+22.4***	+21.6**	- 7.0	-17.1**	5
Temazepam	10	+ 5.9	- 2.5	-12.2*	+ 1.9	2
	30	+14.9*	+ 7.0	-10.6	-16.9***	1
	60	+32.6***	+21.7**	-12.4*	-22.6***	11
Flurazepam	15	+ 6.5*	+10.4*	- 7.9*	- 0.1	9
Flunitrazepam	1.0 ^a	+16.0***	+ 0.2	- 3.0	- 5.5	10

^a After 2 nights; Paired *t*-test comparisons between placebo/active (two-tailed): * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$

active-drug were utilised. In procedure "A" (see Table 1), an initial placebo pre-test was compared to active drug conditions following on immediately from the placebo condition. In procedure "B", a placebo condition (e.g. 4 days on placebo), was compared to an equivalent (non-contiguous) active-drug condition (e.g. 4 days on active drug, Table 1). Leeds SEQ's were completed in the mornings after the initial dose, or after repeated doses (2, 3, or 4) of the drug.

Leeds Sleep Evaluation Questionnaire. The Leeds SEQ described in the appendix has been previously analysed by factor analysis (Parrott and Hindmarch 1978b). The four aspects of sleep around which the questionnaire was devised (Getting to sleep, GTS; Quality of sleep, QOS; Awakening from sleep, AFS; Behaviour following wakefulness, BFW), were found to correspond to four factors in the factor analysis. The mean scores for each of these four aspects of sleep and early morning behaviour are reported from each of the reviewed studies.

Drug Conditions and Regimens. The drug conditions are summarised in Table 1. These represent a variety of psychoactive compounds: sedative-hypnotics (barbiturate or benzodiazepine derivatives, dichloralphenazone), antidepressants (imipramine, nomifensine), antihistamines (promethazine, clemastine), combinations of different drugs, and a CNS stimulant (amphetamine). Dose-regimens and dose-levels are described in Table 1.

Subjects. Subjects were normal volunteers. The age range of all subjects was 18–49 (median 26 years). Males and females were equally frequent. The total number of different subjects in the 13 published studies was 173. Some subjects were used in repeated studies, but only when the drug conditions under investigation were completely different; the degree of overlap between different studies was 0–4 subjects (0%–20% of a subject sample). Subjects were initially screened against the following conditions: history of psy-

chiatric, cardiac, hepatic, or renal disorder. Concurrent medication (excluding contraceptive preparations) and actual or possible pregnancy also precluded participation. Alcohol was not allowed on any day before or after taking a medication. Operating industrial machinery and the driving of motor vehicles during medication periods was also prohibited.

Results

The Leeds SEQ group mean values are listed in Tables 2–4. Table 2 represents data for single nocturnal doses of hypnotics. Table 3 contains data after four consecutive nights on hypnotics. Table 4 represents data from a variety of drug types (antidepressant, antihistamine, drug-combinations), generally after three or four nights on a drug.

The relationship between the ratings of the ease of getting to sleep (GTS) and those of awakening from sleep (AFS) are shown in Fig. 1. This figure represents the group mean GTS and AFS values from Tables 3 and 4. The overall tendency is for any group change in GTS to be accompanied by a parallel but opposite change in AFS. Hypnotics tend to improve GTS and impair AFS, while amphetamine sulphate impairs GTS but improves AFS.

Certain antihistamine agents (promethazine) and drug combinations (amryptiline and chlorthalidoxime) behave as hypnotics, while other drug conditions

Table 3. Sleep evaluation questionnaire values after four consecutive nocturnal doses of various sedative-hypnotic drugs compared to placebo baselines

Drug condition	Dose (mg)	Getting to sleep (GTS)	Quality of sleep (QOS)	Awakening from sleep (AFS)	Behaviour following wakefulness (BFW)	Reference no. (Table 1)
Amylobarbitone sodium	100	+ 9.6**	+15.4**	- 4.9	- 3.3	8
	100	+12.2**	+ 5.9	+ 0.4	- 0.1	10
Dichloralphenazone	1,300	+ 8.9***	+ 5.9	- 8.4*	- 0.1	10
Nitrazepam	5	- 0.4	+10.3	-11.9*	- 6.9*	8
Clobazam	20	+ 9.6*	+ 7.8*	- 0.9	+ 0.4	8
	20	+11.4*	+ 7.3	- 5.3	- 5.6	5
	30 ^a	+ 3.7	+13.8*	- 3.4	- 0.4	6
	30	+12.3**	+ 8.2	-13.2*	-12.3*	5
	40	+15.3***	+26.4***	- 9.0	-21.9***	5
Temazepam	10	+ 2.5	+ 3.7	+ 1.4	- 1.8	2
	20	+16.2*	+ 3.7	- 3.8	- 1.2	2
	30	+20.5*	- 2.0	- 7.1*	- 9.9*	2
	40	+22.7***	+30.7***	-24.9***	-22.2***	11
	60	+21.3***	+22.4***	- 9.9*	-13.1**	11
Flurazepam	15 ^a	+13.0**	+16.7**	- 5.0*	- 1.3	9
Flunitrazepam	1.0	+26.0***	- 2.4	- 6.2	- 5.1	10
Dipotassium clorazepate	15 ^a	+ 3.3	+10.4*	- 2.3	- 0.8	6

^a After 3 nights; paired *t*-test comparisons between placebo/active (two-tailed): * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$

Table 4. Sleep evaluation questionnaire values after various psychoactive drugs compared to placebo baselines

Drug condition	Dose (mg)	Days on drug	Getting to sleep (GTS)	Quality of sleep (QOS)	Awakening from sleep (AFS)	Behaviour following wakefulness (BFW)	Reference no. (Table 1)
<i>Antidepressant</i>							
Imipramine	25 (tds)	4	- 3.8	-14.2***	+ 2.7	+ 1.7	3
Nomifensine	25 (tds)	4	- 5.8	- 7.7**	+ 4.6	- 2.7	3
Nomifensine	25 (tds)	3	- 3.0	- 9.7*	+ 3.1	- 2.4	12
<i>CNS stimulant</i>							
Amphetamine	10 (acute)	1	-19.6***	-13.3*	+16.4*	No data	13
	10 (acute)	1	-18.0***	-11.8	+ 6.5	- 3.0	13
<i>Antihistamine</i>							
Chlorpheniramine	4 (tds)	4	+10.7***	+ 6.5	- 8.8*	- 6.4*	4
Mebhydrolin	50 (tds)	4	+ 5.5	+ 7.2	+ 1.4	- 6.9	4
Clemastine	1 (bd)	4	- 0.4	- 3.9	- 6.4	- 7.8	4
Ketotifen	1 (bd)	4	+ 9.8**	+13.3**	- 1.5	+ 2.0	4
Promethazine	25 (Nocte)	4	+10.7*	+18.9***	- 8.0**	- 3.7	4
<i>Drug combinations</i>							
Nomifensine	25	} (tds) 3	+ 4.6	+ 3.1	- 2.3	- 6.5	12
Clobazam	7.5						
Amytriptyline	25	} (tds) 3	+32.6***	+20.5***	-11.4	-24.3***	12
Chlordiazepoxide	10						
Dichloralphenazone	325	} (Nocte) 4	+11.3*	+13.7*	- 4.7	- 6.3	8
Clobazam	20						
Dichloralphenazone	650	} (Nocte) 4	+ 9.3**	+11.6**	-11.6**	- 8.3**	8
Clobazam	10						

Paired *t*-test comparisons between placebo/active (two-tailed): * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$

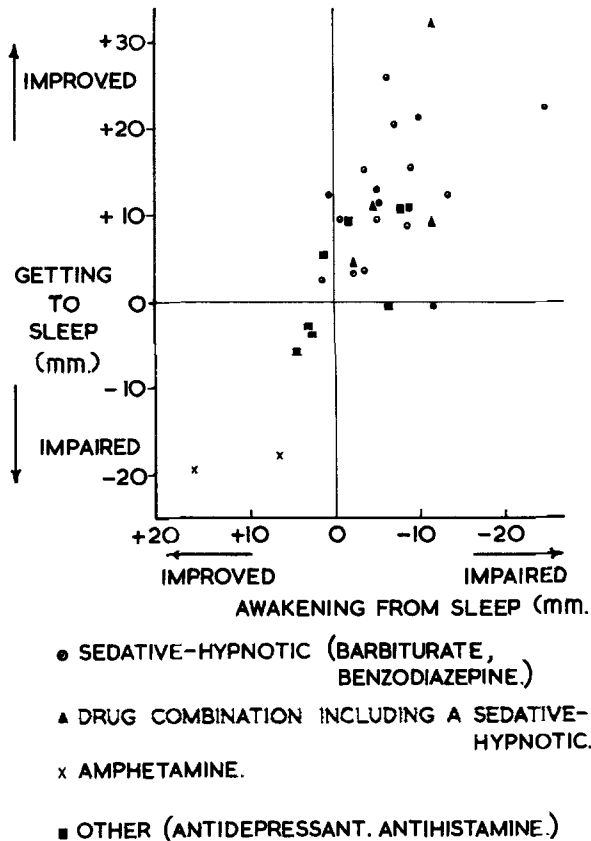


Fig. 1. Leeds Sleep Evaluation Questionnaire; getting to sleep compared to awakening from sleep changes (with reference to placebo baselines)

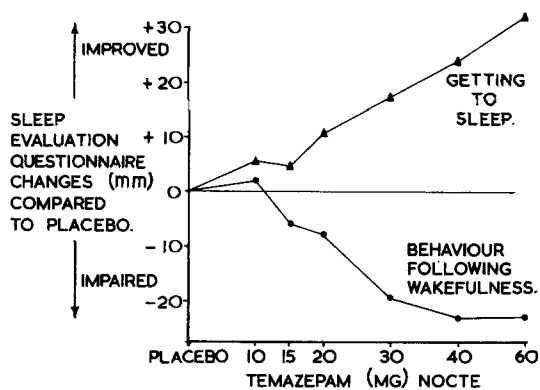


Fig. 2. Dose-response changes on the Leeds SEQ with temazepam; getting to sleep compared to behaviour following wakefulness

(clemastine, nomifensine combined with clobazam) produced little change in GTS or AFS values compared to placebo. A similar relationship to that shown for GTS and AFS scores in Fig. 1 was also demonstrated between the QOS and BFW scores (Tables 2-4).

Dose-response relationships for temazepam, clobazam, and dichloralphenazone are shown in Figs. 2-4.

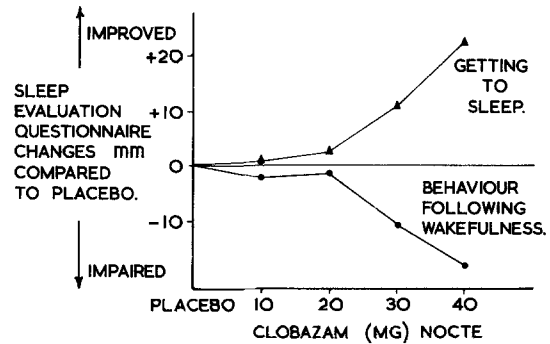


Fig. 3. Dose-response changes on the Leeds SEQ with clobazam; getting to sleep compared to behaviour following wakefulness

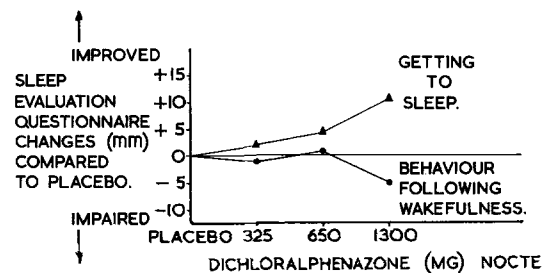


Fig. 4. Dose-response changes on the Leeds SEQ with dichloralphenazone; getting to sleep compared to behaviour following wakefulness

In general, ratings of improvements in the ease of getting to sleep and the concomitant decreases in estimates of the integrity of behaviour following wakefulness are related to increasing dose level.

Discussion

Maxwell (1978) suggested that the utility of visual analogue scales could be indicated from the overall consistency of findings. The most consistent finding from the Leeds SEQ was that group changes in self-reported improvements in the ease of getting to sleep and quality of sleep were generally accompanied by decreases in the ease of awakening and in self-reported levels of early morning alertness.

Bond and Lader (1972, 1973, 1975) concluded that while sedative-hypnotic agents improve sleep, they also lead to "residual effects" on alertness the following morning. They further suggest (Bond and Lader 1975): "Such residual sedative effects may be inescapable attributes of effective hypnotics." Warburton (1975) similarly stated: "Ideally a hypnotic should induce sleep which leaves the patient refreshed and alert the next morning ... At the present time there are no drugs which satisfy these criteria." The present SEQ findings

support these conclusions. The findings also suggest that any drug condition leading to night-time sedation, (even if the therapeutic or target drug effect is not sedation), will produce a decrement in the level of morning alertness and vitality.

Performance consistency on the sleep questionnaire may be gauged by comparing drug conditions which have been replicated in different investigations. Most findings from repeated dose studies were reasonably consistent (Tables 2–4), although some variation was noted in the different significance levels of the replicated conditions. For instance, a single nocturnal dose of nitrazepam (5 mg) produced three similar mean GTS changes when compared to placebo (+6.2, +6.6, +8.9), although only two of these changes were statistically significant at the $P < 0.5$ level. Differences in group composition might account for the different significance levels since sleep changes and drug action may be related to a range of personal characteristics, including age (Březinová and Oswald 1972), personality (Parrott and Hindmarch 1977, 1978a) and drug plasma concentration differences (Curry et al. 1977).

Dose-ranging studies can provide a further indication of the reliability and consistency of the Leeds SEQ findings. The dose-related values have been fairly consistent, with linear relationships between dose level and the extent of self-reported change (Figs. 2–4). Comparisons involving large differences in doses (10, 30, 60 mg temazepam), were however more consistent than comparisons involving smaller dose-level differences (10, 15 mg temazepam).

Dose-response relationships have been reported with some analogue self-rating scales used by other researchers, especially when larger ranges of dose-levels have been involved. Grundström et al. (1979) reported linear dose-response relationships in self-reported drowsiness in a daytime study with nitrazepam (5, 10, and 15 mg) and diazepam (7.5, 15, 22.5 mg). Peck et al. (1977) found increased morning drowsiness with 10 mg nitrazepam compared to 5 mg or 2.5 mg nitrazepam. The two lower nitrazepam doses were intermediate between placebo and nitrazepam, with “sound” sleepers, but not with “light” sleepers. Malpas et al. (1970) reported dose-response effects with nitrazepam 5 and 10 mg, and amylobarbitone sodium 100 and 200 mg. Hart et al. (1976) did not report a dose-response effect with lower doses of amylobarbitone sodium (50 and 100 mg), although they were reported with diazepam (2.5 and 5.0 mg).

The Leeds SEQ has not been used in studies where objective sleep measures have been taken. Analogue self-evaluations have however been compared to objective sleep measures by other workers. Adam et al. (1976) reported higher REM duration and reduced

intra-sleep restlessness (as indicated by EEG changes) with mesoridazine; these were accompanied by an improvement in self-evaluated sleep quality and reduced self-reported morning vitality. McDonald and King (1975) found that scores on a subjective “Complaint of Sleep Disturbance” questionnaire correlated significantly with objective sleep motility readings. Nicholson et al. (1976) reported several significant correlations between subjective self-evaluations and objective EEG changes (e.g. increased stage-3 and -4 sleep, correlating with improvements in self-reported quality of sleep). Subjective sleep evaluations therefore frequently produce results which are consistent with those obtained with more objective (EEG) measures. Lewis (1969) has however demonstrated that there may be systematic distortions in self-evaluated sleep (e.g. estimated sleep onset time) which can only be demonstrated by comparing objective and subjective measures.

Self-evaluations of sleep, as obtained on the Leeds SEQ, can therefore provide consistent and meaningful findings in psychopharmacological investigations. Active drug values compared to placebo, can provide measures for estimating the comparative subjective effectiveness of different sedative-hypnotic agents. They can also indicate when a psychoactive agent, without a target symptom of sedation-hypnosis, is affecting sleep in some way. Although the Leeds SEQ does not provide any objective indication of sleep changes, it can nevertheless provide useful information on subjectively perceived changes in sleep and early morning behaviour, with a reasonable degree of reliability and validity.

Appendix

The Sleep Evaluation Questionnaire

How would you compare getting to sleep using the medication with getting to sleep normally, i.e. without medication?

1. Harder than usual/easier than usual
2. Slower than usual/quicker than usual
3. Felt less drowsy than usual/felt more drowsy than usual

How would you compare the quality of sleep using the medication with non-medicated (your usual) sleep?

4. More restless than usual/more restful than usual
5. More periods of wakefulness than usual/fewer periods of wakefulness than usual

How did your awakening after medication compare with your usual pattern of awakening?

6. More difficult than usual/easier than usual
7. Took longer than usual/took shorter than usual

How did you feel on waking?

8. Tired/alert

How do you feel now?

9. Tired/alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual/less clumsy than usual

Note. A 10-cm line separates the two halves of each question. The questionnaire instructions are: "Each question is answered by placing a vertical mark on the answer line. If no change was experienced then place your mark in the middle of the line. If a change was experienced then the position of your mark will indicate the nature and extent of the change, i.e. large changes near the ends of the line, small changes near the middle."

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