Industrial Health 2010, **48**, 209–214 **Original Article**

Disturbed Sleep and Fatigue as Predictors of Return from Long-term Sickness Absence

Torbjörn ÅKERSTEDT[1, 2]*, Göran KECKLUND[1] and Jan SELÉN[3]

[1]Stress Research Institute, Stockholm University, 10691 Stockholm, Sweden
[2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[3]Statistics Sweden, Stockholm, Sweden

Received June 18, 2009 and accepted September 29, 2009

Abstract: Long-term sickness absence has doubled in Sweden, as has complaints of disturbed sleep. The present study sought to investigate the prospective link between long-term sickness absence and disturbed sleep or fatigue. Sleep and fatigue from a representative national sample was followed up 1.5–2 yr later in terms of return from long-term (≥90 d) and intermediate term (14–89 d) sickness absence. 8,300 individuals participated in the survey, out of which 372 were on long-term and 1,423 were on intermediate term sick leave. The data was analyzed using logistic regression analysis with adjustment for background and work environment variables. Separate analyses were carried out for disturbed sleep and fatigue since they were correlated. The results showed that those with disturbed sleep at the start had an Odds Ratio (OR) of 0.56 (95% Confidence Interval (CI)=0.35–0.90) for returning from long-term sickness absence. For fatigue the results were OR=0.56 (CI=0.34–0.90). Intermediate term sickness absence showed similar, but slightly weaker, results. The results indicate that disturbed sleep and fatigue are predictors of lack of return from long term and intermediate term sickness absence.

Key words: Disease, Prospective, Longitudinal

Introduction

Long term sickness absence (>90 d) doubled in Sweden from 1993 to 2001[1–3], the main reasons being "reaction to stress" or "burnout". Interestingly, the most obvious change in complaints across the corresponding time period has been disturbed sleep[1]. A connection between disturbed sleep and sickness absence seems reasonable since poor sleep has been prospectively related to mortality[4], cardiovascular disease[5] and diabetes[6]. Also, cross sectional studies have found some indications of disturbed sleep among individuals on long term sickness absence[7–9].

In one of the few prospective studies Ihlebaek *et al.*[10] a large increase in sickness absence from 1996 to 2003 in Norwegian national samples failed to find any relation to disturbed sleep or to any other changes in health indicators. Vahtera *et al.*[11], however, found that disturbed sleep after bereavement predicted long-term sickness absence. Also those not bereaved showed a 20% increase in the risk of sickness absence if disturbed sleep was present at the start of the study. Sleep duration was not a predictor. Recently, we showed that disturbed sleep (due to thoughts of work) predicted new cases of long-term sickness absence (≥90 consecutive days), as well as intermediate (14–89 d) sickness absence, while controlling for stress, physical work-load, gender, age and socioeconomic status[12].

If disturbed sleep affects the incidence of long-term sickness absence, also the return to work may have a similar relation. Flodérus *et al.*[7] found such a link for sickness absence in general. The purpose of the present study was to extend our previous work on the incidence of long-term sickness absence[12] to study the return from long-term sickness absence as a function of disturbed sleep (due to thoughts of work).

Since the previous study of incidence of long-term sickness absence also showed that fatigue was a good predictor[12] that variable was included in the present study.

*To whom correspondence should be addressed.
E-mail: torbjorn.akerstedt@stress.su.se

In addition, fatigue, or "non-restorative" sleep is part of the diagnostic criteria of insomnia[13]. Fatigue is also a very prevalent indicator of ill health in the population[14] and it has been related to subsequent sickness absence in several studies[12, 15–17]. However, no information is available on its relation to return to work. The second purpose of the present study was, therefore, to investigate this putative link.

The term "long term" in relation to sickness absence does not have any agreed-upon definition but recent custom in Sweden has been to use a period of ≥90 d of consecutive days off to denote "long term". In addition, also intermediate (14–89 d) sickness absence periods days have been included for comparison. Below that duration the employer carries the economical burden (instead of the health insurance system) and sickness absence figures are not reported to the health insurance system.

Subjects and Methods

Subjects and design

The present analysis was based on the 2001 Work Environment Survey. Just over 14,000 members of the population in employment were selected for the survey, which is a supplement to the continuous Labour Force Survey. The respondents provided answers to introductory questions by phone in October and November 2001. Shortly afterwards they received a postal questionnaire: Most people responded during the same year but a small number of questionnaires were completed in early January 2002. The reference period is generally the last three months, except for a few questions concerning the last twelve months.

The response rate (after phone interview and questionnaire) was 63% (5,235 dropouts). Efforts to compensate for non-response effects by adjusting sample weights were made in a way similar to that of post-stratified weighting of groups. For the present analysis data on sick leave was obtained from the Swedish Social Insurance Administration for each year 2001–2003 for each individual. These data include all sick leave after the first two weeks of each sickness period, that is, for all sickness paid by the social insurance system, but not for shorter sickness absence periods.

Sickness groups were compared using logistic regression adapted to the complex survey design of stratified sampling. The results were adjusted for demographic variables as well as for variables reflecting physical and mental work-load and for work hours. The reason for the work related variables was their strong position as predictors of sickness absence[2, 3].

As regards the outcome "sickness absence", we made calculations on two different outcomes relating to the change from 2001 to 2003. The analysis of the relationship between different predictors and outcome was restricted to subjects that had a registered sick leave in 2001 of 90 d or more (90+) and 14–89 d. The following groups of sickness absence were compared: Those who changed from 14–89 d in 2001 to 0 d in 2003 and those who changed from ≥90 d in 2001 to <90 d in 2003.

Predictors

The following variables were used as main predictors: *Disturbed sleep due to thoughts of work*: one day per week or more often vs less often. *Tired and listless*: one day per week or more often vs less often.

As demographic confounders were used: *Gender* (female vs male), *Marital status* (single vs married/cohabiting), *Age* (16–29 yr and 50–64 yr vs 30–49 yr), *Socioeconomic group* (blue-collar workers: unskilled, skilled; white-collar workers: lower grades, intermediate grades, senior; and self-employed) using unskilled, blue collar workers as reference, *Child/children* at home (yes vs no).

Other predictors included *Awkward work posture*, which was based on a combination of three questions: "working bent-over/leaning forward" 1/4 of the time or more, "working in a twisted position" 1/4 of the time or more, "working with your hands above shoulder height" 1/4 of the time or more. Exposure was considered present if at least one of the questions had a positive response. The reference was "all other". The predictor *Physically heavy work* resulted from a combination of two questions: "physically hard work at least 50 percent of the time" or "lifting 15 kg at a time several times per day at least once a week". At least one positive response was needed for a classification as exposed and the reference was "all other". *Work hours* was categorized into Part-time vs Fulltime (<35 h/wk), *Overtime work* was categorized into yes vs no, with 35–40 h as the cut off depending on the number of fulltime hours indicated. *Shift work* was categorized into yes vs no.

The index *job demands* was based on 4 questions: "Have to skip lunch, work overtime or bring work home" each week or more often, "Work is so stressful that you can't talk or think of other things than work" half the time or more often, "Work demands all my attention and concentration" almost all the time or more often, "Too much to do – agree fully or partly". Two or more positive responses was considered high work demands, with "all others" as reference. *Job control* (low) was constructed from 4 questions: "Can decide how fast to work" half the time or less often, "Most of the time (or never) not able to decide when tasks should be carried out", "Most of the time (or never) not participating in decisions about how my work should be organized", "Have too little or no

influence over my work – agree fully or partly. *Low control* was defined as 3 out of 4 positive answers and the reference was "all others". Lack of *Social support*: "Have the possibility to get support and encouragement from colleagues when work becomes difficult" – never or usually not, "Have the possibility to get support and encouragement from my supervisor when work becomes difficult" – never or usually. Two positive answers were required.

Results

Table 1 shows the number of individuals in the exposed and non-exposed categories of each predictor, as well as the percentage of "cases" with sickness absences with intermediate and long-term duration. The number of cases with long-term sickness absence at the start of the study was 372 and that of the cases with intermediate absence was 1,423.

Table 2 shows the results of the logistic regression using return from long-term sickness absence as the dependent variable. The univariate analysis shows that both disturbed sleep and fatigue had highly significant Odds Ratios for returning from long term sickness absence. Note that both *reduced* the likelihood of returning. Adjustment for background or work-load factors

Table 1. Number of exposed/non-exposed subjects and number and percent of cases returning from intermediate and long-term sickness absence

Exposed/non-exposed categories	Change from 14–89 d to 0			Change from 90+ d to <90		
	Total N	Cases N	Cases %	Total N	Cases N	Cases %
Not disturbed sleep	977	502	51.3	241	131	54.4
Dist sleep	446	166	39.2	131	63	48.1
Not fatigue	624	351	56.3	149	85	57.0
Fatigue	796	315	39.6	240	109	45.4
Male	476	258	54.2	110	57	51.8
Female	980	425	43.4	294	139	47.3
Age 16–29	152	90	59.2	23	14	60.9
Age 30–49 (Ref)	662	324	48.9	173	91	52.6
Age 50–64	641	269	42.0	208	91	43.8
SEG unskilled workers (Ref)	441	194	44.0	134	53	40.0
SEG skilled workers	251	127	50.6	70	36	51.4
SEG lower white collar workers	201	95	49.3	48	25	52.1
SEG interm. white collar workers	340	163	47.9	95	47	49.5
SEG higher white collar workers	72	38	52.8	16	13	81.3
SEG self-employed	150	65	43.3	41	22	53.7
High social support	848	413	48.7	224	103	48.7
Low social supp	608	270	44.4	180	93	51.7
Married/cohabiting	1,102	679	61.6	305	199	65.2
Single	333	210	63.1	99	61	61.6
No children	788	350	44.4	235	110	46.8
Children	668	333	49.9	110	86	78.2
Not heavy physical work	790	393	49.7	211	113	53.6
Heavy physical work	662	288	43.5	191	82	42.9
Not awkward work posture	940	475	50.5	245	123	50.2
Awkward work posture	502	201	40.0	154	71	46.1
Day work	1,109	532	48.0	305	151	49.5
Shift work	347	151	43.5	99	45	45.5
Fulltime work	950	576	60.6	264	102	38.6
Part-time work	417	256	61.4	119	38	31.9
No overtime	1,092	517	47.7	313	156	49.8
Overtime	355	163	45.9	89	38	47.5
Low work demands	585	298	50.9	151	88	58.3
High work demands	871	385	44.2	253	108	42.7
High work control	804	361	44.9	244	115	47.1
Low work control	652	322	54.4	160	81	50.6

Ref=reference category for OR; SEG=socio-economic group. "Total"=total number of subjects in the response category. "Cases"=number of individuals with disturbed sleep or with fatigue. %=number of cases/total number of participants in that response category.

Table 2. Results from logistic regression against return from sickness absence (vs not)

	Unadjusted OR 95%CI	Adjusted* OR 95%CI	Adjusted* OR 95%CI	Adjusted# OR 95%CI	Combined OR 95%CI
14–89 d to 0 d N=1423					
Dist sleep	0.59 0.51–0.80	0.67 0.52–0.88		0.83 0.63–1.10	0.53 0.40–0.70
Fatigue	0.48 0.39–0.60		0.49 0.39–0.63	0.52 0.40–0.68	
≥90 d to 0 d N=372					
Dist sleep	0.55 0.36–0.83	0.56 0.35–0.90		0.70 0.41–1.19	0.46 0.27–0.77
Fatigue	0.51 0.32–0.79		0.56 0.34–0.90	0.65 0.38–1.11	

Odds Ratios and 95% Confidence Intervals. Intermediate (14–89 d) and long-term (≥90 d) absence groups.
*Adjusted for: Age, gender, marital status, children at home, socioeconomic group, heavy physical work, twisted work posture, shift work, overtime work, fulltime/part-time work, work demands, work influence, and social support.
#Adjusted for * plus disturbed sleep *or* fatigue.

increased the OR somewhat (i.e. brought it closer to unity), but it remained significant when using disturbed sleep only or fatigue only as predictors. Entering the two predictors at the same time rendered both insignificant. Combining the two predictors into the same variable resulted in a highly significant effect, predicting reduced probablility of returning to work in individuals with both fatigue and disturbed sleep.

Table 2 also shows the results of the logistical regression using return from intermediate (14–89 d) absence as the dependent variable. The unadjusted analysis shows that both disturbed sleep and fatigue had highly significant Odds Ratios for subsequent return from intermediate term sickness absence. Adjustment for background or work load factors increased the OR somewhat when either of the two predictors was retained in the analysis, but it remained significant. When both were entered in the analysis fatigue remained significant, but disturbed sleep did not. Removing the work-related variables in the analyses above had only marginal effects, that is, the ORs changed with less than 0.08 units and all remained significant. Combining the two predictors into the same variable resulted in a highly significant effect, predicting reduced probablility of returning to work in individuals with both fatigue and disturbed sleep.

The analyses were repeated for each gender separately. For females, long term sickness absence showed OR=0.40 (95%CI=0.23–0.67) for disturbed sleep alone and 0.42 (0.25–0.71) for fatigue alone. That is, both showed a significant reduction of the probability of returning from long-term sickness absence. Intermediate term sickness absence showed 0.75 (0.56–1.02) for disturbed sleep alone and 0.47 (0.35–0.64) for fatigue alone.

In males the values were OR=1.43 (0.42–4.88) for disturbed sleep alone and 1.19 (0.33–4.10) for fatigue alone when predicting return from long-term sickness absence, that is, no significant relation. For intermediate term sickness absence the values were 0.50 (0.29–0.88) for disturbed sleep alone and 0.51 (0.32–0.82) for fatigue alone. In both cases disturbed sleep or fatigue were related to a strong reduction of the probability of returning from long-term sickness absence.

Discussion

The results demonstrate that reporting disturbed sleep or fatigue is associated with an increased risk of not returning to work two years later. This observation was made when either of the two predictors was entered separately. When both were entered at the same time only fatigue in the intermediate absence group remained significant. The reason for this is most likely that the two variables measure the same phenomenon. However, when combined into fatigue and disturbed sleep present at the same time, the effect was pronounced and the ORs for returning to work were reduced and highly significant.

There does not seem to exist any previous observations of this type but, as discussed in the introduction, fatigue is related to *new cases* of short or intermediate term sickness absence[12, 15–17]. Also, burnout, as an extreme form of fatigue, is linked to prospective sickness absence[18]. Logically, it seems reasonable that an inability to muster

energy would be associated with a risk of not returning to work and it has been suggested that sickness absence may be a form of energy conservation[19]. Thus, we suggest that fatigue may well be a major obstacle to returning to a demanding work situation. The fact that it lost explanatory power in the long-term absence group when combined with sleep does not detract from this conclusion since sleep and fatigue apparently share variance and both loose explanatory weight when entered in the analysis together. This is supported by the highly significant result for the combination of fatigue and disturbed sleep into one variable.

With regard to sleep, the present finding that good sleep predicts return from sickness absence agrees with previous findings that poor sleep predicts *entry* into long-term sickness absence[12, 20], as well as later work disability[20]. Like fatigue, poor sleep lost its significant relation to return to work, but for both sickness absence categories and, again, the probable cause of this loss is the overlap between the two predictors.

The strong effect of the combination of poor sleep and fatigue into one variable is also reflected in the diagnostic view of insomnia. Disturbed sleep is not enough for a diagnosis, but also reduced daytime functioning (fatigue, irritation, etc.) is required for a diagnosis of insomnia[13]. Physiologically, fatigued patients on long-term sick leave show pronounced physiological sleep disturbances in terms of more microarousals, reduced sleep stages 3 and 4, and lower sleep efficiency[21]. Burnout patients on sick leave also report extreme sleep reduction towards the end of the process of becoming burned out[22]. It is not clear to what extent such observations can be generalized to long-term sickness absence *per se*. However, sleep and fatigue often correlate highly in cross-sectional studies[23, 24] and reduced sleep duration involves gradual accumulation of sleepiness/fatigue[25]. Furthermore, experimental sleep reduction or studies of insomniacs show clear elevations of fatigue-inducing pro-inflammatory cytokines[26–28]. Proinflammatory cytokines, in turn, appear to be important components of the sickness experience[29]. Thus, even if much data is still missing it seems possible to hypothesize that disturbed sleep may be involved in maintaining fatigue, which may lead to difficulties returning from long-term sickness absence. This question is probably best addressed in studies of interventions or at least in studies that measure both sickness absence and disturbed sleep at two or more points over time.

Importantly, individuals with both poor sleep and fatigue had a reduced probability of returning to work.

It should be emphasized that "disturbed sleep" in the present context refers to disturbed sleep due to thoughts of work. Thus, one can probably not generalize to other causes of disturbed sleep, unless confirmed by other studies. Work environment factors were controlled for in the present study. However, family problems, or presence of disease at the start were not available for analysis and may have affected the results.

When the analyses were carried out separately for each gender the results were weaker and the prediction for disturbed sleep was not significant in males, even if the Odds Ratios were rather similar to that of the female group. However, this may have been caused by the low total N and the lower incidence of long term sickness absence in men, as well as by the lower prevalence of disturbed sleep and fatigue. The current study thus had rather low power and a larger study might yield other results.

The present study has its strength in the prospective design and in the sample being nationally representative. Also, the dependent variable was obtained from official health insurance registers, which regulate the economical compensation for loss of salary while on sickness absence. With the latter as an incentive it seems reasonable to assume that the absence data are reliable. However, limitations like the lack of a more sophisticated measure of disturbed sleep prevents analysis of what aspects of sleep that may have been most important. Also, the selection of covariates may not have been optimal. It would, for example, have been interesting to have included variables like smoking, body mass index (BMI) and alcohol consumption as covariates. However, these were not available in the survey database.

The implications of the present results may be that intervention/treatment to ameliorate sleep difficulties[30] or fatigue[31] might be able to reduce the amount of sickness. However, this remains to be demonstrated in future studies. In summary, the results demonstrate that absence of disturbed sleep and fatigue are predictors of return from long tem sickness absence while controlling for background and work environment variables.

Acknowledgements

Supported by The Swedish Council for Working Life and Social Science and the insurance company Alecta AB. We thank Mr. Alf Andersson at Statistics Sweden for valuable help.

References

1) Statistics Sweden (SCB) (2004) Sjukfrånvaro och ohälsa i Sverige—en belysning utifrån SCB: s statistik. SCB, Stockholm (in Swedish).
2) Lindholm C, Fredlund P, Backhans M (2005) Hälsotillstånd och sjukskrivningsutveckling. In: Den höga sjukfrånvaron — problem och lösningar, Marklund S, Bjurvald S, Hogstedt C, Palmer E and Theorell T

(Eds.), 41–59, Arbetslivsinstitutet, Stockholm (in Swedish).
3) Wikman A (2004) Arbetsliv och sjukfrånvaro. In: Den höga sjukfrånvaron — sanning och konsekvens, Hogstedt C, Bjurvald M, Marklund S, Palmer E and Theorell T (Eds.), 125–51, States Folkhälsoinstitut, Stockholm (in Swedish).
4) Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR (2002) Mortality associated with sleep duration and insomnia. Arch Gen Psychiatr **59**, 131–6.
5) Nilsson P, Nilsson J-Å, Hedblad B, Berglund G (2001) Sleep disturbances in association with elevated pulse rate for the prediction ofmortality — consequences of mental strain? J Intern Med **250**, 521–9.
6) Nilsson PM, Rööst M, Engström G, Hedblad B, Berglund G (2004) Incidence of diabetes in middle-aged men is related to sleep disturbances. Diabetes Care **27**, 2464–9.
7) Floderus B, Göransson S, Alexanderson K, Aronsson G (2005) Self-estimated life situation in patients on long-term sick leave. J Rehabil Med **37**, 291–9.
8) Ohayon MM, Smirne S (2002) Prevalence and consequences of insomnia disorders in the general population of Italy. Sleep Med **3**, 115–20.
9) Doi Y, Minowa M, Tango T (2003) Impact and correlates of poor sleep quality in Japanese white-collar employees. Sleep **26**, 467–71.
10) Ihlebaek C, Brage S, Eriksen HR (2007) Health complaints and sickness absence in Norway, 1996–2003. Occup Med (Lond) **57**, 43–9.
11) Vahtera J, Pentti J, Helenius H, Kivimaki M (2006) Sleep disturbances as a predictor of long-term increase in sickness absence among employees after family death or illness. Sleep **29**, 673–82.
12) Åkerstedt T, Kecklund G, Alfredsson L, Selen J (2007) Predicting long-term sickness absence from sleep and fatigue. J Sleep Res **16**, 341–5.
13) American Academy of Sleep Medicine (AASM) (2005) ICSD — International classification of sleep disorders, revised: diagnostic and coding manual. AASM, Chicago.
14) Wessely S, Chalder T, Hirsch S, Wallace P, Wright D (1997) The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. Am J Public Health **87**, 1449–55.
15) Huibers MJ, Bultmann U, Kasl SV, Kant I, van Amelsvoort LG, van Schayck CP, Swaen GM (2004) Predicting the two-year course of unexplained fatigue and the onset of long-term sickness absence in fatigued employees: results from the Maastricht Cohort Study. JOEM **46**, 1041–7.
16) Bultmann U, Huibers MJ, van Amelsvoort LP, Kant I, Kasl SV, Swaen GM (2005) Psychological distress, fatigue and long-term sickness absence: prospective results from the Maastricht Cohort Study. J Occup Environ Med **47**, 941–7.
17) Janssen N, Kant IJ, Swaen GM, Janssen PP, Schroer CA (2003) Fatigue as a predictor of sickness absence: results from the Maastricht cohort study on fatigue at work. Occup Environ Med **60** (Suppl 1), i71–6.
18) Borritz M, Bultmann U, Rugulies R, Christensen KB, Villadsen E, Kristensen TS (2005) Psychosocial work characteristics as predictors for burnout: findings from 3-year follow up of the PUMA Study. J Occup Environ Med **47**, 1015–25.
19) Hobfoll SE (1998) Conversation of resources theory. Principles and corollaries. In: Stress, culture, and community, Meichenbaum D (Ed.), 51–87, Penum Press, New York.
20) Sivertsen B, Overland S, Pallesen S, Bjorvatn B, Nordhus IH, Maeland JG, Mykletun A (2009) Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study. J Sleep Res **18**, 122–8.
21) Ekstedt M, Söderström M, Åkerstedt T, Nilsson J, Sondergaard H-P, Perski A (2006) Disturbed sleep and fatigue in occupational burnout. Scand J Work Environ Health **32**, 121–31.
22) Ekstedt M, Fagerberg I (2004) Lived experiences of the time preceding burnout. J Adv Nurs **49**, 59–67.
23) Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G (2004) Mental fatigue, work and sleep. J Psychosom Res **57**, 427–33.
24) Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM (2005) Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? J Sleep Res **14**, 245–53.
25) Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep **26**, 117–26.
26) Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP (2004) Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrin Metab **89**, 2119–26.
27) Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP (2004) Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. J Clin Endocrin Metab **89**, 4409–13.
28) Vgontzas AN, Zoumakis E, Papanicolaou DA, Bixler E, Prolo P, Lin H, Vela-Bueno A, Kales A, Chrousos G (2002) Chronic inomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism **51**, 887–92.
29) Dantzer R (2001) Cytokine-induced sickness behavior: mechanisms and implications. Ann N Y Acad Sci **933**, 222–34.
30) Morin CM, Beaulieu-Bonneau S, LeBlanc M, Savard J (2005) Self-help treatment for insomnia: a randomized controlled trial. Sleep **28**, 1319–27.
31) Evengard B, Klimas N (2002) Chronic fatigue syndrome: probable pathogenesis and possible treatments. Drugs **62**, 2433–46.