Sleep disruption in patients with Chronic Pain

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Reader in Epidemiology
Deputy Director, Arthritis Research UK Centre for Epidemiology
MYTH: "Arthritis is just aches & pains as you get older."

Arthritis and Musculoskeletal Conditions in Numbers:

- **10 million** people in the UK are affected, including **15,000** children.
- **£5 billion** NHS spend.
- **7.6 million** working days lost.

*Each year 20% of the general population consults a GP about a musculoskeletal problem.*

- **One in five people** in their 50s has osteoarthritis in their knee.

Arthritis is the biggest cause of pain and disability in the UK:

- More than **76,000** hip replacements.
- Nearly **82,000** knee replacements.
The problem to be addressed: 
Pain doesn’t correlate with disease

35% of RA patients with controlled disease have ongoing pain despite inactive disease

In OA patients there is a poor correlation between disease severity and pain extent, severity and impact

- Between 20 and 80% of patients with knee pain do not have OA
- Up to 50% of patients with severe knee OA do not have pain

Fibromyalgia patients have chronic widespread pain

- There is no clear aetiology
What is the relationship between sleep and pain in people with rheumatic diseases?
Pain clusters within people and rarely presents in isolation at disease sites

<table>
<thead>
<tr>
<th>Pain cluster (n=12,408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>Main pain site</td>
</tr>
<tr>
<td>Mean additional sites</td>
</tr>
</tbody>
</table>

Chronic Widespread Pain

- A useful model of pain
- Common across musculoskeletal disorders
- Largely “unexplained” by disease activity
- Cause is unknown
- Is sleep disturbance the source of pain?

Adapted from pain drawing provided courtesy of L Bateman
Outline

• Sleep and chronic pain
  - The Manchester Epidemiological Studies

• Treatment
  - The MUSICIAN study

• New treatment targets
  - Drivers of non-restorative sleep
  - Pain processing

• Digital epidemiology
  - The QUASAR study
  - Digital challenges
Insomnia and pain: a dose-response relationship

Pain cluster (n=12,408)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>4537</td>
<td>3904</td>
<td>2219</td>
<td>1748</td>
</tr>
<tr>
<td>%</td>
<td>36.6</td>
<td>31.5</td>
<td>17.9</td>
<td>14.1</td>
</tr>
<tr>
<td>Main pain site</td>
<td>None</td>
<td>Knee</td>
<td>Back</td>
<td>All sites</td>
</tr>
<tr>
<td>Mean additional sites</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

Predictors of New-Onset Widespread Pain in Older Adults

Results From a Population-Based Prospective Cohort Study in the UK

John McBeth, Rosie J. Lacey, and Ross Wilkie

The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study

A. Gupta, A. J. Silman, D. Ray\textsuperscript{1}, R. Morriss\textsuperscript{2}, C. Dickens\textsuperscript{3}, G. J. MacFarlane\textsuperscript{4}, Y. H. Chiu, B. Nicholl and J. McBeth
Predictors of incident chronic widespread pain: meta-analysis of the Manchester observational studies

Odds of incident chronic widespread pain

- Life events
- Anxiety
- Somatic symptoms
- Health anxiety
- Depression
- Non-restorative sleep
Percentage of participants repeatedly reporting no pain by number of factors reported as low (from sleep problems, illness behavior, distress, somatization, and life events)
Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study

K. A. Davies¹, G. J. Macfarlane², B. I. Nicholl¹, C. Dickens³, R. Morriss⁴, D. Ray⁵ and J. McBeth¹

<table>
<thead>
<tr>
<th>Sleep factor</th>
<th>Sleep score</th>
<th>CWP persisted (n)</th>
<th>CWP resolved (n)</th>
<th>Univariate model (crude) OR (95% CI)</th>
<th>Univariate model adjusting for age and gender OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Overall</td>
<td>15–20</td>
<td>125</td>
<td>76</td>
<td>Referent</td>
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<tr>
<td></td>
<td>8–14</td>
<td>128</td>
<td>97</td>
<td>1.2 (0.8, 1.8)</td>
<td>1.2 (0.8, 1.8)</td>
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<tr>
<td></td>
<td>0–7</td>
<td>126</td>
<td>127</td>
<td>1.7 (1.1, 2.4)</td>
<td>1.6 (1.1, 2.3)</td>
</tr>
<tr>
<td>No. of days of sleep problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Overall</td>
<td>8–31</td>
<td>159</td>
<td>90</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>1–7</td>
<td>113</td>
<td>111</td>
<td>1.7 (1.2, 2.5)</td>
<td>1.7 (1.2, 2.5)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>107</td>
<td>99</td>
<td>1.6 (1.1, 2.4)</td>
<td>1.7 (1.2, 2.5)</td>
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<tr>
<td>Maintenance</td>
<td>8–31</td>
<td>224</td>
<td>158</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>1–7</td>
<td>117</td>
<td>103</td>
<td>1.2 (0.9, 1.7)</td>
<td>1.2 (0.9, 1.7)</td>
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<tr>
<td></td>
<td>0</td>
<td>38</td>
<td>39</td>
<td>1.5 (0.9, 2.4)</td>
<td>1.4 (0.8, 2.3)</td>
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<tr>
<td>Early wakening</td>
<td>8–31</td>
<td>192</td>
<td>134</td>
<td>Referent</td>
<td>Referent</td>
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<tr>
<td></td>
<td>1–7</td>
<td>118</td>
<td>85</td>
<td>1.0 (0.7, 1.5)</td>
<td>0.98 (0.7, 1.4)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>69</td>
<td>81</td>
<td>1.7 (1.1, 2.5)</td>
<td>1.6 (1.1, 2.4)</td>
</tr>
<tr>
<td>Restorative</td>
<td>8–31</td>
<td>241</td>
<td>170</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>1–7</td>
<td>113</td>
<td>91</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.2 (0.8, 1.6)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>25</td>
<td>39</td>
<td>2.2 (1.3, 3.8)</td>
<td>2.7 (1.5, 4.8)</td>
</tr>
</tbody>
</table>
It is proposed that the "fibrositis" symptom complex be considered a "non-restorative sleep syndrome"
Sleep disturbance

- Alpha-Delta sleep anomaly
- Alpha waking rhythm intruding on delta deep sleep

Problems
- Not specific to chronic widespread pain
  - Other rheumatic diseases
  - Pain free controls
Targeting “sleep” improves patient wellbeing but not pain

- Primary care patients with chronic widespread pain
- Randomised to
  - Treatment as usual (TAU)
  - Telephone CBT (tCBT)
  - Exercise
  - Combined
- Follow up: 6, 9, 24 months
- Primary outcome: Global change in health since entering trial
Independent treatment effects and treatment interactions
(Adjusted for age, sex, Centre, baseline GHQ and CPG)

<table>
<thead>
<tr>
<th></th>
<th>TCBT 6 months</th>
<th>Exercise 6 months</th>
<th>Interaction 6 months</th>
<th>TCBT 9 months</th>
<th>Exercise 9 months</th>
<th>Interaction 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>4.9 (2.0, 12.0)</td>
<td>6.1 (2.5, 14.7)</td>
<td>0.2 (0.1, 0.7)</td>
<td>5.4 (2.3, 12.7)</td>
<td>3.6 (1.5, 8.5)</td>
<td>0.3 (0.1, 0.9)</td>
</tr>
<tr>
<td>9 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trajectories of primary and secondary outcomes in tCBT group

<table>
<thead>
<tr>
<th></th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>% very much better</td>
<td>29.9</td>
<td>32.6</td>
<td>35.4</td>
</tr>
<tr>
<td>% severe pain</td>
<td>4.6</td>
<td>7.1</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Beasley et al 2015
Drivers of unrefreshing sleep in people with musculoskeletal pain

Katie L Druce, John McBeth
Arthritis Research UK Centre for Epidemiology, The University of Manchester

- Pain
- Disability (HAQ)
- Physical activity
- Anxiety & Depression
- Mental fatigue
- Physical fatigue
- Inflammatory Bowel Syndrome (IBS)

Figure 2– Proportion (95% CI) of NRS ≥8 days which could be prevented calculated using population attributable risks
Sleep, pain processing and chronic widespread pain


The effect of sleep deprivation on pain.
According to the majority of the studies, sleep deprivation produces hyperalgesic changes.
Kundermann B, Krieg JC, Schreiber W, Lautenbacher S.

Pain. 2005;115:316-321

Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study

C. Dickens, R. Morriss, J. McBeth


One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain.

Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, Treede RD.
Do nociceptive, neuropathic, and central hypersensitivity mediate the relationship between sleep disturbance and chronic widespread pain?
Study design: prospective cohort study of people free of CWP
Baseline questionnaire

- **Sleep**: Pittsburgh sleep quality index
- **Demographic**: date of birth, sex, SES
- **Pain**: blank body manikin
- **Anxiety and depression**: HAD
- **Physical activity**: Rapid Assessment of Physical Activity
- **Medication use**: total reported
Clinic assessment

- **Quantitative Sensory Testing (QST)**
  - Application of finely calibrated sensory stimuli: pressure, touch, thermal
  - Tests peripheral and central pain processing
  - Results are strongly related to sleep

- **MSK health screen**
  - Arthritis OA, RA, other
  - % body fat (bioelectrical impedance)
  - Obesity ≥ 30% fat for women and ≥ 20% fat for men
QST test battery
All tests conducted at hand (thenar eminence) and foot (dorsum)
| Table 1. Baseline demographics, depression, sleep, aerobic activity, and musculoskeletal health stratified by CWP status at follow up* |
|---|---|---|
| Pain status at follow up | Not CWP N=1,393 (87.2%) | New CWP N=203 (12.7%) | p |
| **Age (years)** | | | 0.001 |
| Range: 34 to 97 | 65.8 (13.5) | 62.5 (10.9) |
| **Sex *** | | | 0.006 |
| Male | 586 (90.7) | 60 (9.3) |
| Female | 806 (84.9) | 143 (15.1) |
| **Deprivation groups in England** | | | 0.872 |
| Range: 28 to 32425 | 17783.9 (10935.3) | 17649.8 (12339.9) |
| **HAD depression scale** | | | 0.001 |
| Range: 0 to 21 | 4.2 (3.1) | 5.6 (1.5) |
| **Pittsburgh Sleep Quality Index** | | | 0.001 |
| Individual scales range: 0 to 3 | | | 0.001 |
| Overall Sleep Quality | 0.8 (0.7) | 1.1 (0.9) |
| Sleep Latency | 0.9 (0.8) | 1.2 (0.9) |
| Duration Of Sleep | 0.9 (0.9) | 1.1 (0.9) |
| Sleep Efficiency | 1.6 (1.3) | 1.8 (1.3) |
| Sleep Disturbance | 1.3 (0.5) | 1.7 (0.6) |
| Need Meds To Sleep | 0.2 (0.6) | 0.4 (0.9) |
| Daytime Dysfunction | 0.6 (0.6) | 1.0 (0.6) |
| **RAPA** | | | 0.001 |
| Range: 0 to 7 | 4.6 (1.9) | 4.1 (1.9) |
| **Number of pain sites at baseline** | | | 0.001 |
| Range: 0 to 29 | 2.0 (2.7) | 4.9 (3.5) |
| **Number of medications** | | | 0.010 |
| Range: 0 to 22 | 2.4 (2.8) | 2.9 (2.9) |
| **Body fat**◊ | | | 0.001 |
| Normal | 580 (90.8) | 59 (9.2) |
| Obese | 812 (85.0) | 143 (15.0) |

HAD = Hospital Anxiety and Depression scale; RAPA = Rapid Assessment of Physical Activity

◊“Obese” classified as % body fat women ≥ 32%, men ≥ 25%.
QST scores at the hand

QST, quantitative sensory testing; CWP, chronic widespread pain; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MPT, mechanical pain threshold; SRF, stimulus response function; ALL, allodynia; WUR, wind up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; *p≤0.05, **p≤0.01 & ***p≤0.001 for t-statistic between parallel profiles of not CWP and CWP.
QST scores at the foot

QST, quantitative sensory testing; CWP, chronic widespread pain; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MPT, mechanical pain threshold; SRF, stimulus response function; ALL, allodynia; WUR, wind up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; *p<0.05, **p<0.01 & ***p<0.001 for t-statistic between parallel profiles of not CWP and CWP.
Mediation analyses

• PSQI predicted new CWP

• Disordered pain processing predicted new CWP
  • Based on Z scores, none were “clinically significant”
  • Associations were not consistent across testing sites

• The relationship with PSQI was not mediated by pain processing
Problems with traditional observational studies

• **PAALS study**
  - Time consuming: 4 years
  - Costly: £1M
  - Methodologically weak: Low uptake and high attrition

• **Not informative**
  - Whether pain processing is the mechanism that explains the relationship between sleep and pain remains unanswered
  - Traditional observational study designs test associations NOT causation
  - Data is not sufficiently granular to examine cause and effect
Digital epidemiology

Mobile, social, real-time: the ongoing revolution in the way people communicate has given rise to a new kind of epidemiology.

Digital data sources, when harnessed appropriately, can provide timely information about exposures, outcomes, and mechanisms.
**Knowledge gap 1:** There is no evidence about which sleep and circadian parameters are critical determinants of RA pain

**Problems**
- The sleep-RA literature has relied on
  - Cross-sectional studies
  - Small sample sizes
  - Relatively crude measurement of subjective sleep

- A few have used polysomnography but lab-based assessments are
  - Time consuming
  - Expensive
  - High attrition
Knowledge gap 2: There is no data on the recurrent and fluctuating nature of sleep problems, pain, fatigue, and mood

Problem
Sleep disruption, pain, fatigue and mood have
• A reciprocal relationship with each other
• High day to day within-person and between-person variation in symptom reporting
Addressing these knowledge gaps

**Use gold-standard home-based sleep and circadian measurement actigraph**

**Sleep:** Latency, wakefulness during the night, duration, fragmentation, circadian amplitude to estimate periodicities and phase shifts of circadian cycles

**Environmental:** Noise, light, humidity, temperature

**Physical activity:** Duration, intensity, % meeting guidelines

**Gather (at least) twice daily measures of symptom and outcome data**

**10 symptoms:** Pain, fatigue, mood, disease severity, morning stiffness, illness beliefs, ...

**HRQoL:** Disease specific and general

**Consensus sleep diary:** Subjective sleep
QUASAR study design

- **Sleep monitor**
- **10 symptoms (AM/PM) Morning sleep diary**

Timeline:
- Day 1
- Day 10
- Day 20
- Day 30
- Day 60

**Data Collection Points**
- **Day 1**
  - Demographics
  - RAPID-3
  - Medications & co-morbidities
  - Sleep (PSQI, SCI, DBAS-16)
  - QoL (WHOQOL-BREF, AIMS2-SF)
  - HADS
  - Coping (ASES-8; CAQ-8)

- **Day 10**
  - RAPID-3
  - Important events
  - WHOQOL-BREF
  - AIMS2-SF

- **Day 20**
  - RAPID-3
  - Important events
  - WHOQOL-BREF
  - AIMS2-SF

- **Day 30**
  - RAPID-3
  - Medications
  - Important events
  - WHOQOL-BREF
  - AIMS2-SF
  - PSQI

- **Day 60**
  - Continuous sleep monitoring
  - Daily symptom tracking
Study deliverables

1. The first clear description of sleep disturbance in people with RA
2. Data on the relationship between sleep and RA pain
3. Recommendations for targets for intervention development studies and future trials
Digital challenges

Ethical challenges
- Data access
- Data sharing
- Privacy

Technical challenges
- Collection and storage of massively large data sets
- New analysis methods

Infrastructure challenges
- Access to vast amounts of storage
- Availability of large clusters of machines for computation
Analysis challenges

Design of algorithms and data structures that are efficient and scalable for processing, mining, and analyzing dynamic and large-scale epidemiologic data

• Identification of a clinically meaningful pain outcome
  • Increase to severe/ very severe pain
  • Increase beyond ‘expected’ pain  

• Identifying causal mechanisms
  • Case time series
  • State space models
  • Causal machine learning

Thomas House, UoM

Antonio Gasparrini, LSHTM
Ricardo Silva, UCL
IBM Research
Digital epidemiology

- Rapid and mass recruitment
- Reduced costs
- Reduced time to address study questions
- Growing number of available exposure, outcome and third variable measurements
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Arthritis Research UK | centre for epidemiology

www.cfe.manchester.ac.uk