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Authors: Eliza E. Moskowitz, Lucin Garabedian, Kimberly Harden, Emily Perkins-Pride, Menilik Asfaw, Candice Preslaski, Kiara N. Liasia, Ryan Lawless, Clay Cothren Burlew, Fredric Pieracci

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A Double-Blind, Randomized Controlled Trial of Gabapentin vs. Placebo for Acute Pain Management in Critically Ill Patients with Rib Fractures

Eliza E. Moskowitz, MD eliza.moskowitz@ucdenver.edu
Lucin Garabedian, PharmD lucin.garabedian@dhha.org
Kimberly Harden, MSN kimberly.harden@dhha.org
Emily Perkins-Pride, MSN emily.perkinspride@dhha.org
Menilik Asfaw, MD menilik.asfaw@dhha.org
Candice Preslaski, PharmD Candice.preslaski@dhha.org
Kiara N. Liasia, MD kiara.liasia@dhha.org
Ryan Lawless, MD ryan.lawless@dhha.org
Clay Cothren Burlew MD clay.cothren@dhha.org
Fredric Pieracci, MD fredric.pieracci@dhha.org

Short Title: Gabapentin for Rib Fractures

NCT: 02856750

From:
Denver Health Medical Center
University of Colorado School of Medicine

**Corresponding Author:**
Fredric Pieracci, MD
Department of Surgery
Denver Health Medical Center
777 Bannock Street, MC 0206
Denver, Colorado 80204
(O) 303-436-4029
(F) 303-436-6572
Eliza.Moskowitz@UCDenver.edu

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Abstract

Introduction: Achieving adequate pain control for rib fractures remains challenging; prescription of alternatives to narcotics is imperative to curtail the current opioid epidemic. Although gabapentin has shown promise following elective thoracic procedures, its efficacy in patients with rib fractures remains unstudied. We hypothesized that gabapentin, as compared to placebo, would both improve acute pain control and decrease narcotic use among critically ill patients with rib fractures.

Materials and Methods: Adult patients admitted to the trauma surgery service from November 2016 – November 2017 at an urban, Level I trauma center with one or more rib fractures were randomized to either gabapentin 300 mg thrice daily or placebo for one month following their injury. Daily numeric pain scores, opioid consumption, oxygen requirement, respiratory rate, and incentive spirometry recordings during the index admission, as well as and one-month quality of life survey data were abstracted.

Results: Forty patients were randomized. The groups were well matched with respect to age, gender, prior narcotic use, tobacco use, and prior respiratory disease. Although the median RibScore did not differ between groups, the gabapentin group had a higher median number of ribs fractured as compared to the placebo group (7 vs. 5, respectively). Degree of pulmonary contusion and injury severity score were similar between groups. Use of loco-regional anesthetic modalities did not differ between groups. Daily numeric pain scores, opioid consumption, oxygen requirement, respiratory rate, and incentive spirometry recordings were similar between
both groups. No benefit was observed when adding gabapentin to a multi-modal analgesic regimen for rib fractures. There were no instances of pneumonia, respiratory failure, or mortality in either group. Hospital and intensive care unit length of stay were similar between groups. Both overall and chest-specific quality of life was equivalent between groups at one month follow-up.

Conclusions: In this group of critically ill patients with rib fractures, gabapentin did not improve acute outcomes for up to one month of treatment.
Introduction

Rib fractures are present in thirty percent of patients with significant chest trauma [1], and account for more than half of all blunt thoracic injuries [2]. Fractures of multiple ribs can lead to significant pulmonary compromise [3], and may result in chronic pain, dyspnea, and lost quality of life (QoL) [4]. Adequate analgesia for patients with rib fractures is imperative to mitigate the risks of atelectasis, pneumonia, respiratory failure, and death [1, 5, 6]. Analgesia has been accomplished traditionally using a combination of oral and intravenous narcotics, with narcotic analgesics remaining the mainstay of pain management therapy for traumatic rib fracture related pain [7]. The use of narcotic analgesics is associated with various risks including over sedation, delirium, constipation, addiction, tolerance, and misuse.

Over the past 20 years, the opioid crisis has reached epidemic proportions in the United States. The United States consumes 80% of the world’s prescription of narcotics, despite only possessing 4.4% of the world’s population [8]. Moreover, misuse of prescription opioid analgesics account for nearly half a million emergency department visits [9]. Opioid misuse results in nearly 200,000 deaths annually [9], nearly quadruple the number of deaths reported secondary to narcotic misuse in 1999 [10]. Trauma patients are particularly vulnerable to opioid misuse [11], underscoring the importance of alternative analgesics.

“Multi-modal” pain therapy for rib fractures, involving a combination of non-narcotic adjuncts, locoregional anesthesia, non-steroidal anti-inflammatory drugs (NSAIDS), and surgical stabilization of rib fractures has gained favor in the last decade [12]. One potential non-narcotic adjunct, Gabapentin (Neurontin, Pfizer NYC, New York, NY, USA), is a structural analogue of Gamma-aminobutyric acid (GABA), an inhibitory amino acid that exerts presynaptic control of afferent fibers. It is a potent anticonvulsant drug that has been proven to reduce visceral
nociception in animals, and has been shown to decrease postoperative pain in patients undergoing thoracic [13], abdominal [14], and orthopaedic [15] surgical procedures. The mechanism by which it does so, however, remains elusive [16]. Its established efficacy for analgesia, combined with its favorable safety profile, limited side-effect profile, and wide dose ranging capabilities have led to its wide spread off-label use as an analgesic adjunct [17] for many pain syndromes [18].

A retrospective study has suggested improved pain control with gabapentin for patients following elective thoracic surgery [19]. However, the efficacy of gabapentin in the management of patients with rib fractures has not been studied. The objective of this trial was to evaluate the efficacy of gabapentin in the acute setting for analgesia in patients with rib fractures. We hypothesize that gabapentin, as compared to placebo, will improve acute pain control and decrease narcotic use.

**Methods**

We conducted a randomized, double-blind trial of gabapentin vs. placebo. Adult patients (age > 17 years) with traumatic rib fractures admitted to the Trauma Surgery service from November 2016 to November 2017 were eligible for enrollment. Inclusion criteria were ≥ 1 rib fractures requiring hospital admission, and study enrollment within 24 hours of initial injury. Exclusion criteria were: pregnancy, intubation, age >65 years, inability to tolerate oral medication, renal or hepatic impairment, allergy or hypersensitivity to gabapentin, traumatic brain injury, inability to obtain consent from patient or surrogate, and patient refusal. The age cutoff of 65 was chosen due to Food and Drug Administration recommendations to consider dose
reduction for elderly patients due to decreased gabapentin plasma clearance and resultant higher risk of side effects. [20]

Following informed consent, patients were randomized to either the gabapentin or placebo group within 24 hours of their admission. Patients then received either gabapentin 300 mg or placebo thrice daily for 30 days following their injury. Gabapentin was obtained from Amerisource Bergen, Inc. (Denver, CO). Placebo and matching active capsule were then compounded by Pencol pharmacy (Denver, CO). Patients, nursing staff, and investigators were blinded to treatment group until the data analysis phase of the study. Randomization was performed in a block pattern using a pre-determined randomization log generated by the Denver Health Research Pharmacy, which tracked patient assignment.

All patients were prescribed additional non-narcotic analgesia according to an institutional guideline, including acetaminophen 650 mg orally every 6 hours and ibuprofen 600 mg orally every 6 hours, unless contra-indicated. Locoregional anesthesia (i.e., continuous intercostal nerve block catheter or thoracic epidural catheter) was placed at the discretion of the treatment team, and based upon the patient’s response to other analgesic therapies, contra-indications, and patient preference. Surgical stabilization of rib fractures was considered based upon a standardized institutional guideline for patients with 1) flail chest, 2) 3 or more severely displaced fractures or 3) loss of greater than 30% of thoracic volume [21]. Use of each of these analgesic adjuncts was abstracted.

Demographic information included: age (years), gender, history of asthma or tobacco use, body mass index (BMI) (kg/m²), and pre-injury narcotic use. Injury severity was assessed using the mechanism of injury, Injury Severity Score (ISS), total number of rib fractures, RibScore (a radiographic scoring system assessing the presence of ≥6 rib fractures, bilateral fractures, flail
chest, ≥3 bicortical fractures, first rib fracture, and presence of fractures in the anterior, lateral and posterior distributions. Higher RibScores have been found to be associated with development of pneumonia, acute respiratory failure, and need for tracheostomy [22], Blunt Pulmonary Contusion 18 Score [23], pneumothorax, sternal, scapula, clavicle, spine, and long bone fractures, solid organ injury, and need for surgery during the index admission.

The primary outcome variable was the daily average numeric pain score (NPS), range 0-10, obtained by averaging hourly scores recorded by nursing over the 24 hour period for seven days or until discharge, whichever occurred first. Additional inpatient outcomes assessed daily were the opioid consumption, oxygen requirement (L), respiratory rate (breaths per minute), and best incentive spirometry recording (mL). Opioid requirements were standardized based upon conversion of medications into equi-analgesic dosing (Table 1) [24]. Additional outcomes included ICU and hospital length of stay, need for mechanical ventilation, development of pneumonia, and mortality.

At a one month follow-up visit, subjects were administered a 4-question QoL questionnaire, which includes a combination of the American Chronic Pain Association Quality of Life Scale and a modified version of the RAND 36 Questionnaire that incorporates dyspnea-specific questions from the Chronic Obstructive Pulmonary Disease Assessment Tool [25]. Overall QoL ranges from 1 (worst) to 11 (best) and several pulmonary specific variables ranged from 0 (least symptomatic) to 5 (most symptomatic).

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Continuous data are expressed as mean (range) and categorical data as number (%). For data analysis, the means of continuous variables were compared using the 2-tailed t-test. The proportions of categorical variables were compared using the chi squared test unless expected
cell counts were less than ten, in which case Fisher's exact test was used. Statistical significance was defined as $p<0.05$. An *a priori* power analysis was performed using $\alpha=0.05$ and $\beta=0.80$, and hypothesizing that gabapentin treatment would decrease the average daily NPS from 6 to 5. The parameters chosen for the power analysis yielded a sample size of 20 per group. Based upon our institution’s trauma registry data, as well as a projected 10% study declination rate, we estimated that one year would be necessary to accrue the total sample of 40 subjects. FDA approval for the use of Gabapentin as an Investigational New Drug (IND) was obtained prior to beginning this study. The Institutional Review Board of the University of Colorado approved the study. The trial was registered with clinicaltrials.gov (NCT02856750) and conducted in accordance with the CONSORT statement [26].

**Results**

Study flow is shown in Figure 1. Forty patients were randomized, with twenty having received gabapentin and twenty having received placebo. The average number of doses received while inpatient vs. total possible inpatient doses was 19 vs 21 for the gabapentin group (91%) and 24 vs 27 (89%) for the placebo group ($p=0.36$). Group demographics and injury patterns are summarized in Table 2. The groups were well matched with the exception of a higher mean number of ribs fractured for the gabapentin group as compared to the placebo group (7 vs. 5, respectively).

Uses of additional, non-narcotic analgesics are summarized in Table 3. The majority of patients did not receive either thoracic epidural or pain catheters. These percentages did not differ according to study group. Surgical stabilization of rib fractures was only performed in one patient in the placebo group.
Daily outcomes are depicted in Figure 2. At no point in time did the NPS differ between groups. Furthermore, opioid consumption, respiratory rate, oxygen requirement, and incentive spirometry did not differ between groups over the one week period. The average total opioid equivalents over the index admission was 10.0 for the placebo group (range 0-39) and 9.6 for the gabapentin group (range 0.5 – 29, p=0.87). Although the IS values did remain approximately 100 mL higher for the gabapentin group as compared to the placebo group for each day, this difference did not reach statistical significance at any point.

No patients developed pneumonia, respiratory failure, or died. Hospital length of stay was similar between the two groups (median of 8 days for both groups; p=0.97). ICU length of stay was similar between the two groups (median of 3 days for both groups, p=0.6). There were no serious adverse events deemed to be related to the study drug in either group.

Results from the one month QoL survey are summarized in Table 6. Complete data were available for 29 of the 40 subjects (73%). Neither overall QoL nor any of the pulmonary-specific sub-categories differed between groups.

Discussion

In this randomized, placebo-controlled trial of patients admitted to the trauma surgery service with rib fractures, we did not find a benefit to adding gabapentin to a standardized, multi-modal analgesic regimen. During the index admission, there were no significant differences in daily NPS, opioid use, pulmonary complications, and length of stay. Furthermore, there was no difference in one month QoL.

Gabapentin, although developed originally as an anti-epileptic, has been used increasingly as an analgesic. Treatment of acute, sub-acute, and chronic pain in the age of the
opioid epidemic has proven challenging for physicians, and gabapentin has been used with increased frequency, as an “off label” analgesic in these capacities, with many believing that it is being over-prescribed [18]. To date, the FDA has approved gabapentinoids to treat pain related to fibromyalgia, post-herpetic neuralgia as well as neuropathic pain secondary to diabetes or spinal cord injuries[18]. However, despite these narrow indications, in 2016, gabapentin was the 10th most commonly prescribed medication in the United States [18].

In the surgical population, a meta-analysis demonstrated that gabapentin improves the analgesic efficacy of opioids, resulting in a mean 35% reduction in total opioid consumption over the first 24 hours postoperatively, and a significant improvement in measured pain [27]. Another meta-analysis of pre-operative gabapentin administration among surgical patients across many disciplines (abdominal breast, ear, nose and throat, gynecological, orthopaedic, and spine), also found improved inpatient pain scores and reduced 24-hour opioid consumption among patients who received gabapentin as compared to controls [28]. Numerous studies have also been conducted to evaluate the effect of postoperative gabapentinoid administration on long-term pain, with mixed results[29].

Although not studied specifically in rib fractures alone, Silhoe et al studied gabapentin’s utility in a small cohort of patients who had either undergone chest surgery, or had sustained blunt force trauma to the chest. Seven of eight patients (88%) who had undergone thoracotomy reported pain relief, and 9/12 (75%) of the blunt force trauma victims reported pain relief at a median of 22 weeks’ time, using starting doses of 300 mg BID with up-titration to 300 TID as needed. Despite these findings, the authors cautioned against routine prescription pending completion of a randomized placebo-controlled trial [13]. More recently, in the context of a prospective randomized study of elective thoracotomy patients who received a 600 mg dose of
preoperative gabapentin versus placebo as an adjunct to standard narcotic analgesics, Kinney et al observed no difference in terms of pain scores, postop nausea/vomiting, respiratory depression or pain 3 months post-operatively [30].

Mixed results have been reported within the orthopaedic literature in terms of gabapentin’s ability to reduce narcotic requirements and improve pain in the context of long bone fractures. Mirkheshti et al. reported decreased narcotic requirement with the application of gabapentin as an adjunct, using a daily dose of 300 mg [15]. However, a randomized controlled trial performed last year in which patients undergoing tibial fracture surgery received either gabapentin, paracetamol, or placebo, demonstrated no difference between gabapentin and paracetamol in terms of ability to decrease mean opioid requirements postoperatively. [31]

Gabapentin’s use as in multimodal pain regimens for controlling acute pain secondary to rib fractures remains common [32], and recent consensus guidelines recommend consideration of gabapentin as part of multi-modal analgesia [32, 33]. However, these recommendations were assigned a low grade in recognition of poor data on the topic.

Despite dosing similar to the aforementioned studies, our trial did not observe any benefit to adjunctive gabapentin therapy. The gabapentin and placebo groups were well matched with respect to demographics, comorbidities, overall injury severity, and severity of rib fractures as measured by the RibScore. Furthermore, adjunct analgesic modalities, such as loco-regional anesthesia, were used with similar frequencies between groups. Therefore, it is unlikely that the lack of effect of gabapentin was due to this group being either sicker at baseline or less likely to receive additional therapies for their rib fractures.

Risks of gabapentin administration include dizziness, drowsiness, fatigue, viral infection, thinking abnormalities, abnormal gait, skin rash, blurred vision, and cough. [14], [16],[17]. We
did not observe development of these adverse events in our study cohort. There were no serious adverse events deemed to be related to the study drug in either group.

Despite our efforts to standardize therapies such as opioids, administration of analgesics was left to the discretion of the care team, and most commonly involved interactions between the subjects and their nurse requesting medications (both narcotic and non-narcotic) that were prescribed to be administered PRN. However, because the trial was both randomized and blinded, it is unlikely that this would confound our findings.

An additional consideration is attrition bias. Specifically, our study was powered for 40 subjects and, as patients were discharged from the hospital, the overall number of patients being compared dropped, particularly for days 5-7 post injury, for which each group had as few as 6 subjects remaining. However, the effect size of gabapentin vs. placebo remained very small, if any and, in certain cases such as the NPS, the gabapentin group actually appeared to report a higher mean NPS as compared to the placebo group. Finally, the percent of patients lost to follow up at the time of our one month QoL survey was less than reported in the trauma literature [34] [35].

One final consideration involves the dosing schema that we selected for the gabapentin. Although most patients are started on 100 mg thrice daily for analgesic purposes, we selected 300 mg TID (900 mg daily) to maximize the potential for effect. The actual maximum dose of gabapentin is 1,200 mg TID (3,600 mg daily); however, this large dose should be achieved only after slow upward titration [17]. We elected not to up-titrate the dose in response to patient’s reported pain level in order to maintain uniformity across both the placebo and the control group in terms of what was being administered. Furthermore, treatment failure with gabapentin is
typically not considered until after 4 – 8 weeks of therapy, and this trial limited follow up to one month after surgery.

Despite these potential limitations, there was no benefit observed for gabapentin over placebo in this population of patients with rib fractures. Potential concerns with routine gabapentin prescription for patients with rib fractures involve both cost and side effects, including potential sedation in traumatic brain injury patients [36]. While gabapentin is relatively inexpensive ($1.33 per 300 mg capsule), based on our data, this $120 per month is an unnecessary expense.

In conclusion, we observed no benefit to adding gabapentin to a multi-modal analgesic regimen for rib fractures, using a dose of 300 mg thrice daily for 30 days. Although these data do not support the routine use of gabapentin for this indication, there may be specific patients for whom it is effective, and there may be unappreciated benefit at both higher doses and for longer courses of therapy. Based on these data, our group of trauma surgeons has agreed to suspend its use for this indication pending further research. We similarly caution against incorporation of gabapentin into standardized multi-modal analgesic protocols for patients with rib fractures at the current time.
No conflicts of interest.

References

Figure 1: Study Flow

Patients screened during study period (158)

Inclusion Criteria Met (59)

Not Enrolled (19)

Patient Refusal (13)

Already on Gabapentin (2)

Other (4) (Pregnant, Nursing, Incarcerated)

Enrolled and randomized (40)

Allocated to Gabapentin (20)

Allocated to Placebo (20)
Figure 2: Effects among 40 patients with rib fractures who received or did not receive Gabapentin

Results: Incentive Spirometry

Results: Opioid Consumption

Results: Numeric Pain Score

Results: Respiratory Rate

Results: Oxygen Requirement
Table 1: Narcotic Equivalents (Adapted from Barr et al[37])

<table>
<thead>
<tr>
<th>Narcotic</th>
<th>Dose</th>
<th>Unit</th>
<th>route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>mg</td>
<td>IV</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>mg</td>
<td>PO</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100</td>
<td>mcg</td>
<td>IV</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>mg</td>
<td>IV</td>
</tr>
<tr>
<td>Morphine</td>
<td>30</td>
<td>mg</td>
<td>PO</td>
</tr>
<tr>
<td>Oxycodone (Percocet)</td>
<td>20</td>
<td>mg</td>
<td>PO</td>
</tr>
<tr>
<td>Hydrocodone (Vicodin)</td>
<td>30</td>
<td>mg</td>
<td>PO</td>
</tr>
</tbody>
</table>
Table 2: Patient demographics and injury pattern

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=20)</th>
<th>Gabapentin (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 (21-64)</td>
<td>48 (20-65)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (70%)</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>26 (17-36)</td>
<td>26 (18-42)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>6 (30%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Pre-injury narcotic use</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Injury Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>16 (4-34)</td>
<td>12 (1-24)</td>
</tr>
<tr>
<td>Total rib fractures</td>
<td>5 (3-12)</td>
<td>7 (2-15)</td>
</tr>
<tr>
<td>RibScore</td>
<td>1 (0-6)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>BPC18</td>
<td>4 (0-9)</td>
<td>4 (0-9)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>10 (50%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Sternal fracture</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Scapula fracture</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Clavicle fracture</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Spine fracture</td>
<td>5 (25%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Long bone fracture</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Solid organ injury</td>
<td>5 (25%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Surgery during index admission</td>
<td>8 (40%)</td>
<td>11 (55%)</td>
</tr>
</tbody>
</table>
Table 3: Additional pain modalities utilized during index admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Gabapentin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>16 (80%)</td>
<td>11 (55%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Epidural</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pain catheter</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td>0.45</td>
</tr>
<tr>
<td>SSRF</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Table 4: Quality of life one month after injury

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=14)</th>
<th>Gabapentin (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working currently/Working prior to injury</td>
<td>7/11 (63%)</td>
<td>9/13 (69%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Overall QoL (1-11)</td>
<td>9 (5-11)</td>
<td>8 (4-11)</td>
<td>0.46</td>
</tr>
<tr>
<td>Sub-categories (0-5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1.07 (0-3)</td>
<td>0.40 (0-2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Chest mucous</td>
<td>0.64 (0-2)</td>
<td>0.53 (0-3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>1.21 (0-3)</td>
<td>0.60 (0-3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Walking up stairs</td>
<td>1.29 (0-5)</td>
<td>1.00 (0-5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Activities at home</td>
<td>1.14 (0-5)</td>
<td>1.33 (0-5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Leaving home</td>
<td>0.71 (0-3)</td>
<td>0.53 (0-3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.50 (0-2)</td>
<td>0.90 (0-4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Energy</td>
<td>0.64 (0-2)</td>
<td>0.80 (0-4)</td>
<td>0.70</td>
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