# Refractory Chronic Migraine: Long-Term Follow-up Using a Refractory Rating Scale

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## INTRODUCTION

Refractory Chronic Migraine (RCM) is often a debilitating illness, with an enormous impact on quality of life. The Refractory Headache Special Interest Section (RHSIS) of the American Headache Society (AHS) has provided a forum for physicians on this crucial topic. Chronic migraine occurs in approximately 2% of the population[1]; the prevalence of RCM is unknown.

Much work has been accomplished on the definition of RCM.[2] A summary of the current proposed criteria are listed (see Table I). The definition is a continuous work in progress.[3] Long-term outcomes for those with RCM have not been investigated. In addition, there is a range of severity among the RCM patients. For clinical and research purposes, it is important to categorize the RCM patients according to severity.

This study assessed pain and quality of life (QOL) in RCM patients over a 10 year period. A novel RCM "severity rating scale" was used for the evaluation of these patients.

## METHODS

### Design and Patient Selection

This was a retrospective chart review of 129 RCM patients. RCM was diagnosed according to criteria suggested by the Refractory Headache Special Interest Section of the AHS (Table 1).

### *Table 1*.  REFRACTORY CHRONIC MIGRAINE CRITERIA (PROPOSED)[3]

1. Patient has diagnosis of chronic migraine (or migraine).
2. Patient has failed adequate trial of at least two out of four drug classes
   a. Anticonvulsants
   b. Beta blockers
   c. Tricyclics
   d. Calcium channel blockers
3. Patient has modified lifestyle and eliminated triggers
4. Patient has failed abortive medications, including:
   a. Triptans and DHE
   b. NSAIDs and combination analgesics
5. There may be modifiers:
   a. With or without medication overuse
   b. With significant disability

**Inclusion criteria:** RCM patients greater than 18 years old as of the year 2000. The patients were followed at our headache center during the years 2000 to 2010, and must have remained at the clinic for that time. 129 pts., with an average age of 49 (108F, ages 19-72, and 21M, ages 31-69), were assessed.

**Refractory Scale**

A refractory scale of this author's design was utilized for assessment. The scale ranges from 2 (least severe) to 10 (most severe). See Table 2.

*Table 2.* **REFRACTORY SCALE** (2-10, 10=most severe)

1. Refractory to preventives = 2 points (refractory to preventives is determined by RHSIS[3] and Silberstein[4] criteria).
2. Refractory to abortives = 2 points (determined by RHSIS[3] and Silberstein[4] criteria).
3. Greater than 10 years of chronic migraine= 1 point (chronic migraine defined according to International Headache Society (IHS) criteria[5]).
4. 25 or more days of headache per month (on average) = 1 point.
5. Two of the following associated medical conditions: irritable bowel syndrome (IBS), fibromyalgia, temporal mandibular dysfunction (TMD), chronic pelvic pain, painful bladder syndrome, and chronic fatigue = 1 point. These syndromes were defined according to guidelines established by the various specialty organizations. Patients had to have been diagnosed using the standard criteria.[6]
6. Psychiatric comorbidities of the following types: severe Axis I (affective disorder), or any Axis II (personality disorder) = 1 point. These were diagnosed utilizing guidelines established in DSM-IV.[7]
7. Disability (work and/or home) = 1 point. The pt. had to demonstrate moderate to severe disability with poor functioning for at least 6 months. Disability was assessed by various means, including interviews with the patient and family. A VAS functioning scale was utilized.
8. Medication overuse headache= 1 point. Criteria established by the IHS were utilized.[5]

The patients were assigned a number (2 thru 10) as of the year 2000, and this assignment of severity was not reassessed after the initial date.

The severity groupings were as follows: score of 2, 3, or 4: mild RCM.
score of 5, 6, 7: moderate RCM.
score of 8, 9, 10: severe RCM.

**Outcome Measures**

Quality of Life (QOL): QOL was measured by adding pain, functioning, and mood scores (each on a 1-10 scale, with 1 = best, 10 = worst). The QOL rating scale ranged from 3 (best) to 30 (worst). Pain was assessed via a visual analog scale of 1-10, (10=worst). Functioning was determined by the level of the work and/or home activities. Mood determinates included depression, anxiety, and insomnia. These were assessed using DSM-IV criteria.

Pain Level: Pain was assessed using a visual analog scale, 1-10 (10=worst).

**Statistics**

SPSS (Statistical Package for Social Sciences v17 for Windows) was used for the statistical analyses. Difference scores for QOL1-QOL2 and pain ratings time1-time2 were calculated. In order to analyze if these pre-post scores differed across the three pain severity groups (mild, moderate, severe), a One-way Analysis of Variance (ANOVA) was conducted. To determine if treatment was significantly effective in

decreasing level of pain and improving quality of life, pre-post paired samples *t*-tests were calculated for each severity group. Finally, Cohen's effect size formula [(mean1-mean2)/(the average of standard deviation1 + standard deviation2)] was used for paired samples *t*-tests.

**RESULTS**

N=129 patients (108 F, ages 19-72, 21M, ages 31-69, average age 49). The patients were initially categorized according to the refractory scale (2-10, 10=most refractory). QOL (Table 3) and pain level (Table 4) were assessed as of the year 2000, and also as of the year 2010.

*Table 3.* **QUALITY OF LIFE:  Year 2000 vs. 2010**

| Initial Degree of Refractoriness | Initial QOL in 2000 (3-30, 30=worst) | Final QOL in 2010 | % Improvement in QOL, 2000-2010 |
|---|---|---|---|
| Mild (2-4 on refractory scale) N=24: average #=3.79 | 13.2 | 8.6 | 35% p<.001, Effect Size(ES) = 2.07 |
| Moderate(5-7) N=67: average #=6.04 | 15.8 | 10.8 | 32% p<.001, ES = 1.30 |
| Severe(8-10) N=38: average #=9.02 | 21.6 | 14.4 | 33% p<.001, ES = 1.50 |

For the mild patients, 66% improved by 30% or more in QOL during the 10 years. In the moderate group, 57% improved by 30% or more, and in the severe group 61% improved by 30% or more.

QOL over 10 years was the same, or worse, in 4% of mild pts., 16% moderate, and in 18% of severe pts..

ANOVA revealed significant mean change score (time1-time2) differences for QOL ratings between severity groups, $F_{(2,126)}=4.31, p=.02$. Bonferroni post hoc results showed that improvements in QOL after treatment were significantly larger for the severe group compared to the mild group (p=.045) and for the severe group relative to the moderate group (p=.03). Change scores for the mild to moderate group did not significantly differ.

*Table 4.* **PAIN LEVEL: Year 2000 vs. 2010**

| Initial Degree of Refractoriness | Initial Pain Level(2000) (1-10, 10=worst) | Final Pain Level(2010) | Change(%) from 2000-2010 |
|---|---|---|---|
| Mild(2-4) N=24 | 7.8 | 4.3 | -45% P<.001, Effect Size(ES)=2.55 |
| Moderate(5-7) N=67 | 7.7 | 4.5 | -42% P<.001, ES=1.30 |
| Severe(8-10) N=38 | 8.6 | 5.5 | -36% P<.001, ES=2.16 |

In the mild group, 80% of the pts. had a decline in pain levels of 30% or more over the 10 years. In the moderate group, 72% had a decline in pain levels of 30% or more. The severe group had 71% of pts. report a decline in pain of 30% or more over the 10 years.

Pain levels were the same, or worse, over the 10 years in only 4% of mild pts., 15% of moderate, and in 18% of the severe pts.  ANOVA findings for the change scores in pain ratings failed to yield any between severity group differences.

*Table 5*. **OVERALL RESULTS (ACROSS ALL GROUPS)** N=129

| | |
|---|---|
| Initial QOL(2000) = 17 <br> *(3-30 scale, 30=worst)* | Final QOL(2010) = 11.4 <br> *(33% improvement)* |
| Initial pain level(2000) = 7.96 <br> *(1-10 scale, 10=worst)* | Final pain level(2010) = 4.76 <br> *(40% improvement)* |

60% of pts. had an improvement in QOL by 30% or more (over the 10 years)

15% of pts. saw no change, or suffered a decrease, in QOL

73% of pts. had pain levels decrease by 30% or more

14% of the pts. reported no improvement, or an increase, in pain levels over the 10 years

Paired samples *t*-tests were conducted for each severity group between assessment periods. Regarding the mild group, QOL ratings significantly improved after treatment, $t(23) = 11.88$, p<.001, *ES*(Cohen's d) = 2.07, and pain ratings significantly decreased, $t(23) = 10.15$, p<.001, *ES* = 2.55.

In the moderate group, QOL significantly increased, $t(66) = 9.95$, p<.001, *ES* = 1.30, and pain levels significantly decreased, $t(66) = 13.36$, p<.001, *ES* = 2.26. Finally, results for the severe group revealed a statistically significant increase in QOL after treatment, $t(37) = 9.51$, p<.001, *ES* = 1.50, and a significant decrease in pain levels, $t(37) = 10.42$, p<.001, *ES* = 2.16. Overall, the results suggest that the treatment was effective in improving quality of life and reducing level of pain for all severity groups.

<p align="center"><em>Table 6.</em> <strong>MEDICATIONS</strong></p>

The following medications were reported to be beneficial by the refractory patients. To be listed, the patient must have found the medication helpful for their pain, and to have continued on the medication for at least 6 months.

|  | Opioid | Frequent Triptans, 4+ per week | Butalbital | Onabotulinum-toxinA | Stimulant | Other |
|---|---|---|---|---|---|---|
| Mild N=24 | 10 42% | 11 46% | 3 13% | 6 25% | 4 17% | 2 8% |
| Moderate N=67 | 44 66% | 23 34% | 11 16% | 9 13% | 5 7% | 6 9% |
| Severe N=38 | 27 71% | 6 16% | 8 21% | 6 16% | 6 16% | 4 11% |
| Total N=129 | 81 63% | 40 31% | 22 17% | 21 16% | 15 12% | 12 9% |

Overall, the medications that helped the most over the 10 years included: opioids (63%), frequent triptans (31%), butalbital compounds (17%), and onabotulinumtoxinA (16%).

**DISCUSSION**

This study categorized refractory chronic migraine patients according to a unique refractory rating scale. The pts. were evaluated as of the year 2000, and again 10 years later. Most (60%) of the pts. had at least a 30% improvement in QOL, while 73% also experienced a 30%(or more) improvement in pain levels. While the severe pts. also improved over 10 years, they still had significantly lower QOL, and higher pain scores than the mild or moderate patients. In this refractory group, opioids and frequent triptans were the most commonly used medications.

The refractory rating scale presented here is an initial attempt to classify RCM pts. according to severity. A refractory scale may be beneficial for both clinical and study purposes. Patients with mild RCM will generally be easier to treat than those with severe RCM. Therapeutic studies on those with RCM may be less likely to succeed if the patients have severe RCM vs. milder RCM. The individual components of the scale reflect various elements of refractoriness, including comorbidities. This author awarded more weight to "refractory to preventives" (2 points) or "refractory to abortives" (2 points) than to the other components (1 point each), primarily because refractory to preventives or abortives are central hallmarks of RCM.

Because the plasticity of the brain may be an important factor in refractoriness, it is important to include the length of time of headache (selected for this study at >10 years). The average number of headache days per month is important, with 25+ days probably being more refractory than 15 to 24. Associated medical comorbidities often occurring in those with chronic migraine were included. These conditions may complicate treatment, and add to refractoriness. For this study, we included the following: IBS, fibromyalgia, TMD, chronic pelvic pain, painful bladder syndrome, and chronic fatigue.

Psychiatric comorbidities, commonly seen in RCM patients, certainly complicate treatment. Significant abuse in childhood may predispose one to RCM. Important comorbidities include anxiety, depression, the bipolar spectrum, personality disorders, somatization, and post-traumatic stress disorder.[8,9] For this study, severe DSM-IV Axis I (affective disorders), or any Axis II (personality disorders) were considered important in refractoriness.[7]

Disability should be a part of a refractory scale. Those who function at a low level, at work or at home, often are more resistant to treatment. Patients exhibit a wide range of coping and resilience. Resilience is a combination of nature and nurture; one can almost predict resilience based upon the shape of the serotonin transporter gene. This author believes that disability, or a chronically low level of functioning, renders it less likely that the RCM will improve. The level of functioning should factor into a refractory rating scale.

Medication overuse headache (MOH) is a remarkably complicated concept; MOH must be distinguished from medication overuse without resulting headache. It can be exceedingly difficult to determine who has MOH.[5] For this study, we used IHS guidelines as to MOH. MOH does add to refractoriness and resistance to treatment, and should be included in a refractory scale.[5]

The medications utilized by patients in this study included: opioids, (usually long-acting opioids), frequent triptans, butalbital, onabotulinumtoxinA, and stimulants. The author has published on most of these subjects.[10] [11] [12] [13] For refractory chronic migraine patients, it often takes a combination of medications to achieve even minimal benefits. Many of the patients in the study took two or more of the listed medications.

Refractory chronic migraine constitutes a small but important subset of migraine patients. For clinical and study purposes, it is helpful to categorize RCM patients as to the degree of refractoriness. After 10 years, the severe patients remained behind the other groups regarding quality of life and level of pain. However, over the 10 years, all of the groups (mild, moderate, severe) improved regarding quality of life and level of pain. This initial attempt to create a refractory rating scale should be refined and improved with further study and research.

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## ABSTRACT

**Background: RCM** is often associated with disability and a low quality of life (QOL). There is a need to categorize these patients according to severity. We utilized a unique RCM severity rating scale (RS), tracking the clinical course over ten years.

**Methods:** Retrospective chart review. **Inclusion:** RCM patients >18 years, who were patients at the headache center for at least ten years, 2000-2010. 129 patients (108F, ages 19-72 and 21M, ages 31-69). Using a **refractory scale**, the patients were given an initial severity score, 2 to 10 (10=worst). The scale= a) refractory to preventives, 2 points. b) refractory to abortives, 2 points. One point added for each: c) >10 years of H/A. d) 25+ days/month of H/A. e) two of the following associated medical conditions: IBS/fibro/painful bladder syndrome/chronic pelvic pain/TMD/fatigue. f) significant psychiatric issues (severe Axis I, any Axis II(personality disorder)) g) disability (work or home). h) medication overuse headache. The patients were grouped according to the refractory scale: 2-4=mild, 5-7=moderate, 8-10=severe**. QOL**: determined by adding pain, functioning and mood scores (3-10, 30=worst). **Pain Level**: VAS, 1-10 (10=worst).

**Results:** As of the year 2000, 129 RCM patients were given a severity score(2 to 10). 24pts.=mild, 67=mod., 38=severe. QOL: for **mild** pts., avg. QOL improved 35% from 2000 to 2010. 66% improved 30% or more. For **mod**. pts., avg. QOL improved 32%, while 57% improved 30% or more. **Severe** group: avg. QOL improved 33% and 61% improved 30% or more. QOL was the same, or worse, in 4% of mild pts., 16% mod., and 18% severe pts. At the end of the study, QOL levels were still significantly less in the severe group than in mild or mod. groups. **Pain Level**(1 to 10): for **mild pts**., pain scores declined over 10 years by avg. 45%; 80% of mild patients had pain levels decline 30% or more. **Moderate pts.:** pain declined an avg. of 42%; 72% had pain levels decline 30% or more. **Severe pts**.: pain declined avg. of 36%; 71% had a decrease of 30% or more. **Overall**, 73% had a 30% or more decline in pain. **Pain** was the same, or worse, in 4% of mild, 15% of mod., and 18% of severe pts. **Pain** levels remained higher in the severe group. **MEDS**: Overall, the meds that helped significantly over the 10 years included: opioids(63%) frequent triptans(31%), butalbital(17%), onabotulinumtoxinA(16%), stimulants(12%), and other "various" preventives(9%).

**Conclusion: RCM** pts. were rated using a refractory rating scale, and their course followed over 10 years. QOL and pain improved over the ten years in all groups. In the severe group, **QOL** and pain improved, but after 10 years still lagged behind the mild and moderate patients**. Opioids** and (frequent) **triptans** were the most commonly utilized meds.