



The importance of real-world evidence (RWE) using the example of a diclofenac pain relief gel and a xylometazoline nasal spray

Markus Zieglmeier

Real-world evidence (RWE) studies are gaining increasing importance in medical research because they investigate drug therapy use under everyday conditions. Two recent RWE studies in the field of self-medication exemplify the added value that this methodology offers for the evaluation of medicinal products.

Real-world evidence (RWE) in medicine refers to clinical knowledge regarding the use, potential benefits or risks of a medical product in everyday life, without the strict inclusion and exclusion criteria of randomised clinical trials (RCTs). The combination of RCTs and RWE enables a more comprehensive understanding of the efficacy and safety of medical interventions and is increasingly used in all phases of research.

RWE study with Voltaren pain relief gel 1.16% and Voltaren pain relief gel forte 2.32%

International and national guidelines recommend topical nonsteroidal anti-inflammatory drugs (NSAIDs) as the treatment of choice for acute musculoskeletal pain, such as sprains and strains, osteoarthritis of the knee and fingers and acute back pain [1–4]. A recently published large RWE study evaluated, for the first time, patient experiences and usage patterns of diclofenac pain relief gels in everyday life [5].

Retrospective analysis

During the one-year study period, data stored in the pharmacy software from almost 4 million customers were screened for Voltaren pain relief gel (1.16% diclofenac) and Voltaren pain relief gel forte (2.32% diclofenac). The preparations were mainly dispensed to elderly, multimorbid patients, a target group that is underrepresented in clinical trials. Of the nearly 100,000 data sets, approximately 42.7% contained Voltaren pain relief gel and about 65.3% Voltaren pain relief gel forte. According to this, 8% of the patients received both concentrations during the study period. The following dispensation patterns were evident:

- The average age of the patients was 72.0 years (range: 18 to 85+), with the majority being female (60.9%).
- During the study period, 70.8% of the patients purchased only one pack of diclofenac pain relief gel.
- Fewer than 1% of the patients received an additional oral NSAID within seven days of receiving diclofenac pain relief gel.
- The majority of the patients did not switch to another topical pain treatment during the analysis period, indicating high patient satisfaction.
- A total of 74.3% of patients also received medication for existing cardiovascular diseases and 35.4% for gastrointestinal complaints. 30.9% of patients received treatment for both conditions.

Prospective, longitudinal survey

Using a questionnaire, 467 patients were questioned about the intensity of their pain and functional impairment at the time of purchase of Voltaren pain relief gel 1.16% or Voltaren pain relief gel forte 2.32% as well as about their satisfaction with the treatment four and twelve weeks thereafter.

Pain was assessed on a numerical rating scale (NRS) and categorised into four pain intensities: no pain (NRS 0), mild pain (NRS 1–3), moderate pain (NRS 4–6) and severe pain (NRS 7–10). At week 4, 48.6% of the patients, who were in the severe pain category at baseline, transitioned to a milder pain category. By week 12, as many as 58.7% of the patients, who had initially suffered severe pain, transitioned to a lower pain category (Fig. 1).

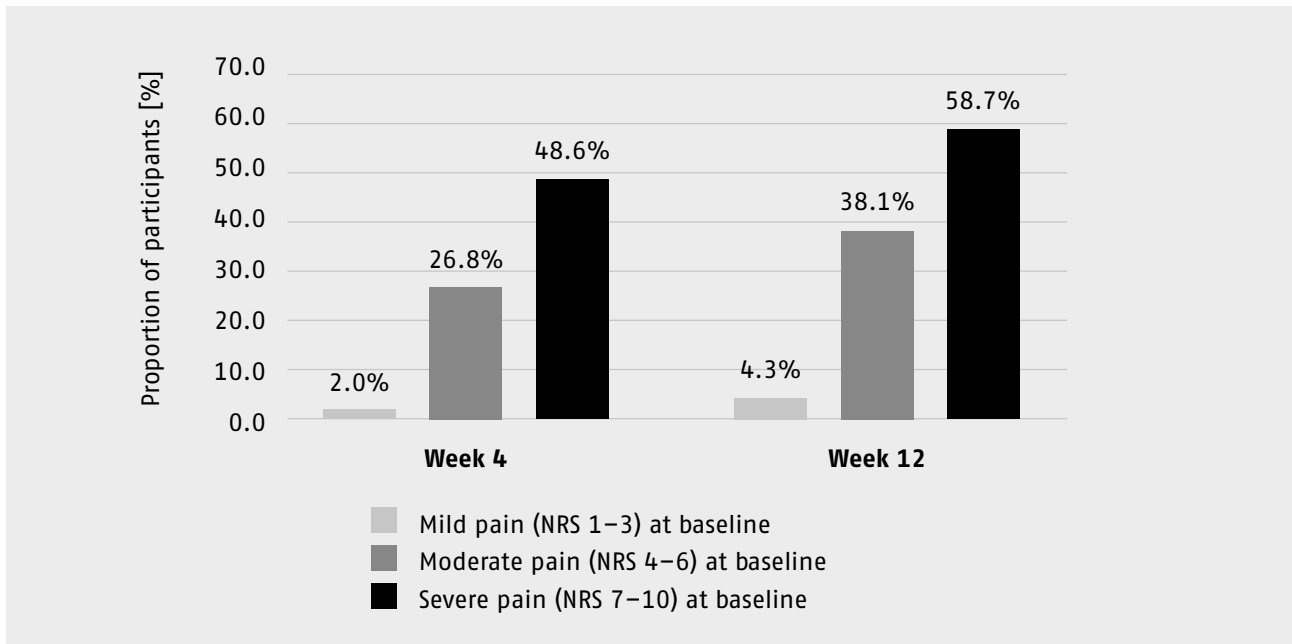


Fig. 1. Percentage of patients, who moved from their respective pain category at baseline to a less severe pain category at weeks 4 and 12, respectively. Ratings are based on the numerical rating scale (NRS) for pain (see text) [5].

At baseline, most participants were at least moderately impaired in the following areas: daily activities such as eating, dressing, sleeping, personal hygiene (78.4%), housework and errands (69.8%), physical activities (79.5%), and social activities (48.0%). Limitations in everyday life improved over the course of the study in the vast majority of patients (Fig. 2).

More than three quarters of the patients were "satisfied" or "very satisfied" with the results of topical treatment with diclofenac pain relief gel (77.2% at week 12). Reasons for satisfaction were that independence is preserved, the product is easy to use and the performance of daily activities is made easier. The present observational study demonstrates that adequate pain treatment improves the affected patients'

ability to participate in everyday life, thereby improving their quality of life. In addition, reducing movement restrictions can promote the healing process and prevent poor posture. Especially for multimorbid patients, topical application is an excellent treatment option compared to oral analgesics and anti-inflammatory drugs, as it significantly reduces the risk of systemic side effects and interactions.

RWE study with Otriven 0.1% nasal spray

An RWE study is the first to examine the quality of life of people with colds during treatment with Otriven nasal spray with 0.1% xylometazoline hydrochloride [6]. A total of 136 participants were asked to complete the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) questionnaire

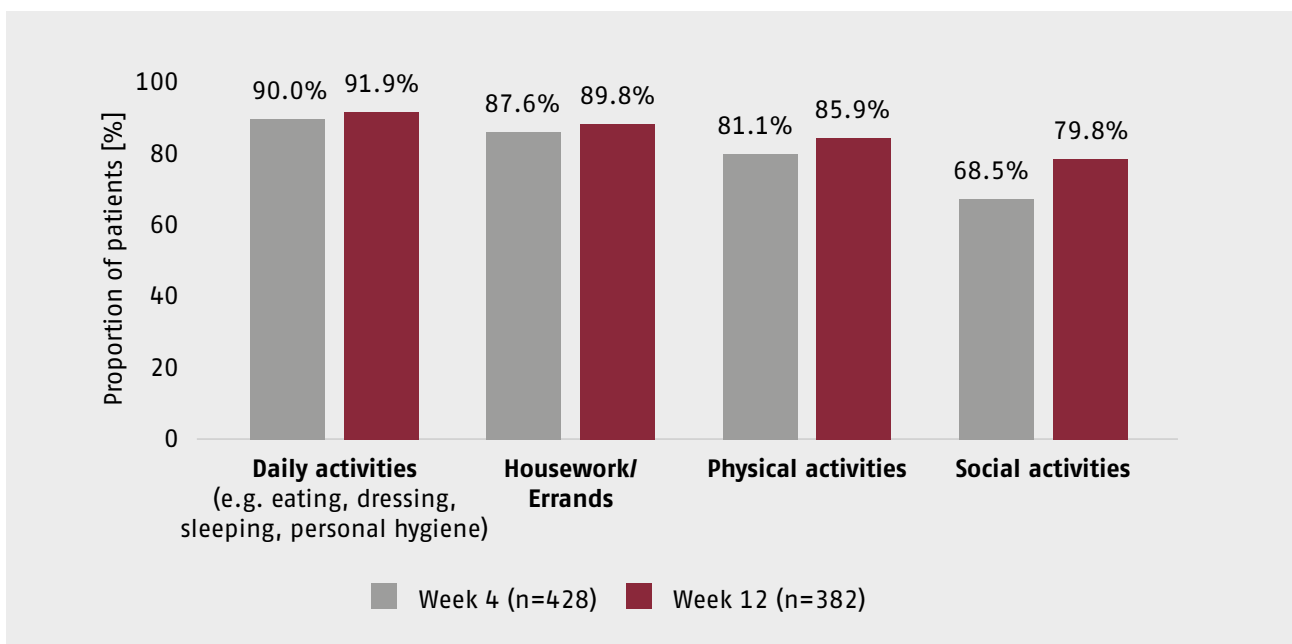


Fig. 2. Proportion of patients reporting improvements in their performance of daily activities [5]

via an app on their smartphone at the start of the study and on each treatment day (maximum 7 days), for the purpose of documenting the course of the cold symptoms and the impairment of daily activities in the preceding 24 hours. The questionnaire consists of a total of 21 questions, which included nine questions about quality of life. In this study, the WURSS-21 was supplemented by additional questions concerning the quality of life (e.g. snoring, energy levels and sensory perception), in order to better assess the effects of the decongestant nasal spray on everyday life (Tab. 1).

Both the cold symptoms and the limitations in everyday life (quality of life) were assessed on a numerical scale from 0 = no symptoms or limitations to 7 = severe symptoms or limitations. Included in the study were study participants with at least moderate nasal congestion (≥ 5 points) and another cold symptom of at least mild intensity (≥ 3 points) at baseline. The most serious complaints at the start of the study were nasal congestion (5.5 ± 0.09 points), breathing difficulties (5.3 ± 0.14 points), reduced energy (5.2 ± 0.14 points), lack of motivation (5.2 ± 0.14 points), reduced quality of sleep (4.9 ± 0.16 points), feeling tired (4.9 ± 0.16 points) and impaired sense of smell (4.8 ± 0.16 points).

Already on day 1, the symptom of nasal congestion was significantly reduced compared to baseline ($p < 0.01$) and continued to decrease over the course of the study. With the last application, the symptom had reduced by 68.1% (from 5.5 ± 0.09 to 1.8 ± 0.16 points), corresponding to very mild to no symptoms. The WURSS-21 Total Symptom Score, which includes all ten questions assessing cold symptoms (including nasal congestion, sore throat and cough), improved significantly from day 2 up to the end of the study (64.8% at the end of the study versus baseline).

The impact of treatment with 0.1% xylometazoline hydrochloride on overall quality of life is evident from the WURSS-21 Total QoL Domain Score. It includes nine

Tab. 1. Quality of life (QoL) categories used in the study with individual quality of life factors [6]

Quality of life category	Individual quality of life factors
Sleep quality	<ul style="list-style-type: none"> Good sleep (WURSS-21) Snoring
Vitality	<ul style="list-style-type: none"> Reduced energy Reduced motivation Feeling tired (WURSS-21) Alertness, attentiveness
Physical activity	<ul style="list-style-type: none"> Respiratory problems (WURSS-21) Walking, climbing stairs, exercising (WURSS-21) Performing daily activities (WURSS-21)
Social activity	<ul style="list-style-type: none"> Interaction with others (WURSS-21) Self-confidence in dealing with people
Sensory perception	<ul style="list-style-type: none"> Sense of smell Sense of taste
Other QoL factors	<ul style="list-style-type: none"> Uncertainty regarding the sound of one's own voice Working inside the house (WURSS-21) Working outside the house (WURSS-21) Living your personal life (WURSS-21) Thinking clearly (WURSS-21)

questions on quality of life (see factors marked "WURSS-21" in Table 1) and improved significantly from the first day (day 1) of using the decongestant nasal spray (Fig. 3).

In order to more clearly understand, in which areas of everyday life the decongestant nasal spray improves quality of life, five distinct categories were established using questions from the WURSS-21 questionnaire and the eight supplementary questions concerning quality of life. The categories "Sleep quality", "Vitality", "Physical activity", "Social activity" and "Sensory functions" (Tab. 1) were calculated for each treatment day. Here, the first four categories demonstrated significant improvement starting as early as day 1, which continued to increase throughout the study. The

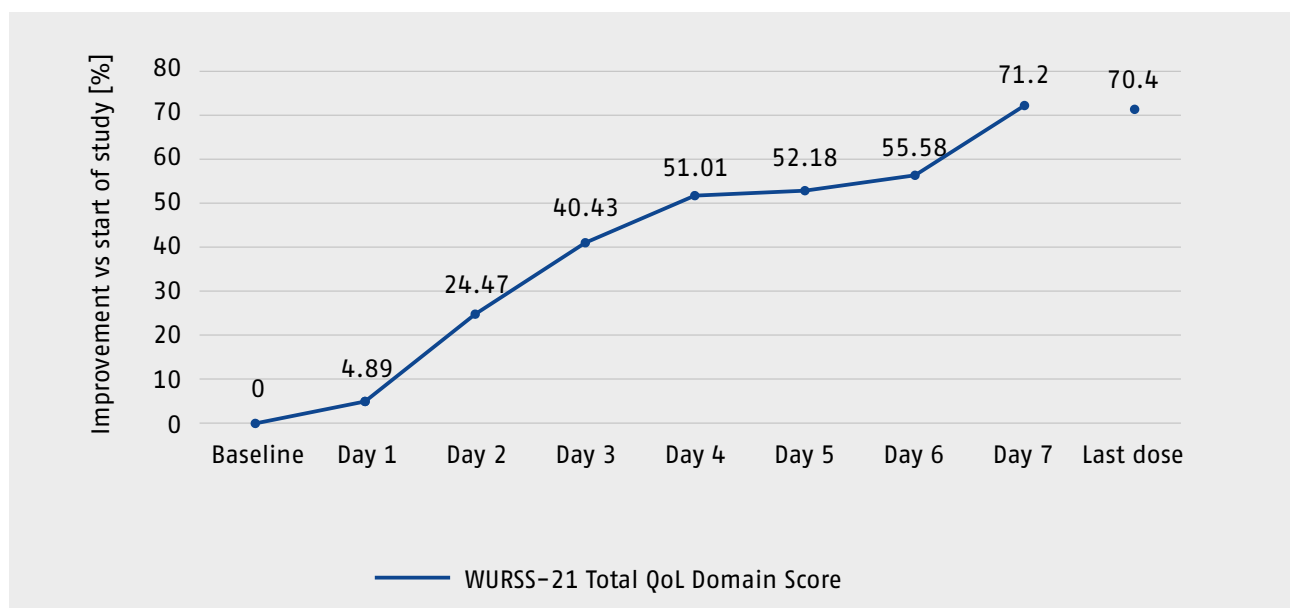


Fig. 3. WURSS quality of life assessment. The percentage improvement compared to baseline is shown (day 1, $p < 0.05$; days 2 to 7 and last dose, $p < 0.0001$). The improvement compared to the start of treatment is 71.2% after one week. [6]

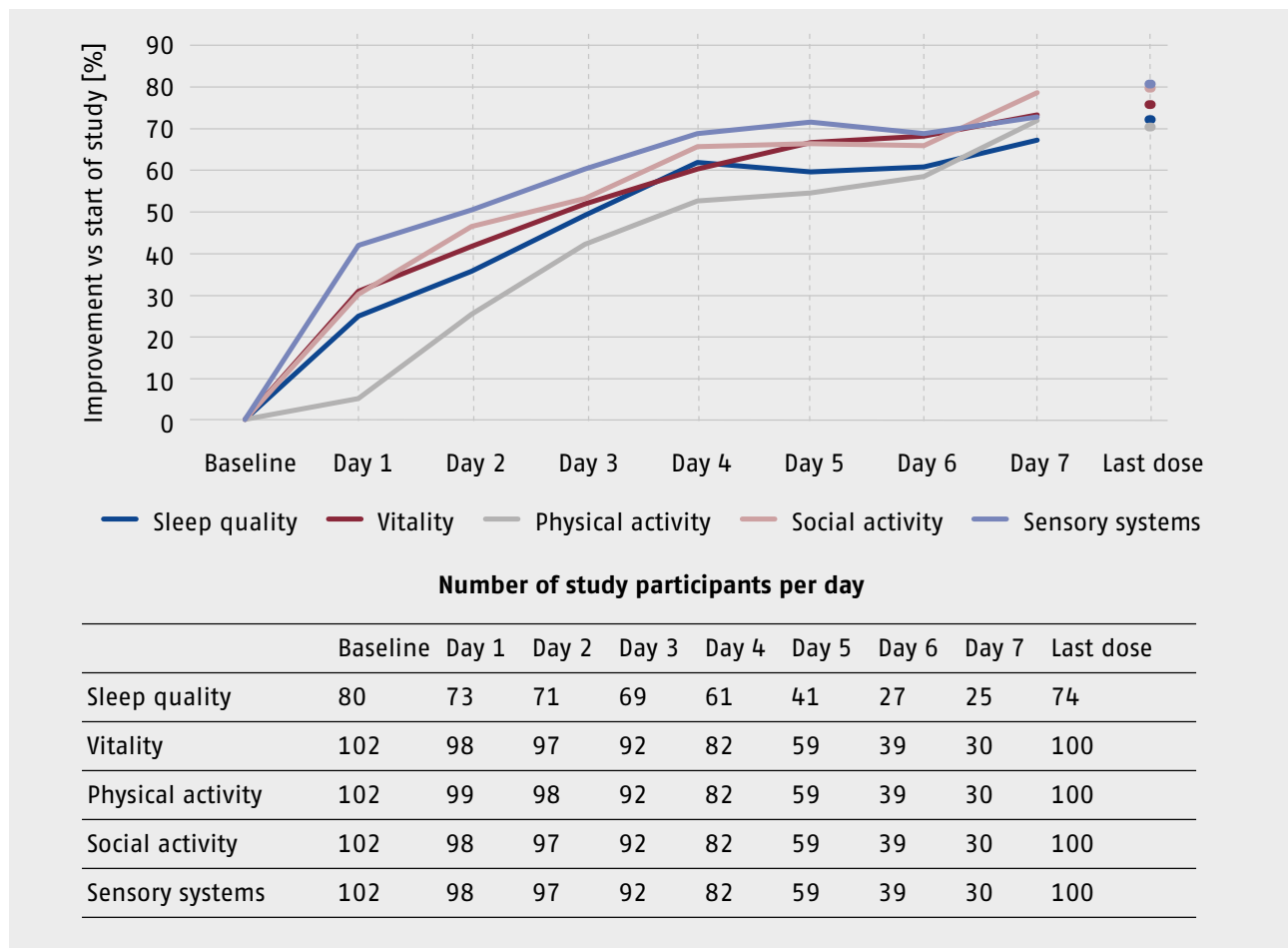


Fig. 4. Significant percentage improvements were observed in sleep quality ($p < 0.0001$), vitality ($p < 0.0001$), physical activity ($p < 0.0808$, from day 2 $p < 0.0001$), social activity ($p < 0.0001$) and sensory systems ($p < 0.0001$) compared to baseline [6]. Most study participants only used the nasal spray until day 5 (last dose).

category "Physical activity" showed a notable improvement from day 2 up to the end of the study (Fig. 4).

The treatment was only carried out for as long as necessary. The decongestant nasal spray was used by 58% of the patients for a maximum of five days. On day 7, 30% of patients administered the last dose. More than 90% of the participants in this study reported being satisfied or very satisfied with the product and would use xylometazoline hydrochloride 0.1% again. This RWE study clearly demonstrated that the effect extends far beyond improved nasal breathing. The improvement in nasal breathing affected all areas of life. The sleep quality in particular could be of central importance, not only for the regeneration of the immune system but also for the vitality and, consequently, the quality of life of the patients.

Conclusion

As demonstrated by these two studies, RWEs significantly contribute to evidence generation, as in addition to randomised controlled trials, they provide valuable insights into the use of medications under real-life everyday conditions.

Literature

1. National Institute for Health and Care Excellence (NICE). Osteoarthritis in over 16s: diagnosis and management (2022). <https://www.nice.org.uk/guidance/ng226> (accessed 19/06/2024).
2. Kloppenburg M, Kroon FP et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Annals of the Rheumatic Diseases* 2019;78:16-24. <https://ard.bmj.com/content/annrheumdis/78/1/16.full.pdf> (accessed 19/06/2024).
3. Bruyère O, Cooper C et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis—From evidence-based medicine to the real-life setting. *Seminars in Arthritis and Rheumatism* 2016;45(4):3-11. <https://www.sciencedirect.com/science/article/pii/S0049017215002887?via%3Dihub> (accessed 19/06/2024).
4. Bannuru RR, Osani MC, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis and Cartilage* 2019;27(11):1578-1589. [https://www.oarsijournal.com/article/S1063-4584\(19\)31116-1/fulltext](https://www.oarsijournal.com/article/S1063-4584(19)31116-1/fulltext) (accessed 19/06/2024).
5. Maihöfner C, de Haas A, et al. Patients' experience and utilization patterns of diclofenac gel in Germany: a real-world study with a prospective longitudinal survey and a retrospective analysis of pharmacy data. *Current Medical Research and Opinion* 2023;39:1649-61. doi:10.1080/03007995.2023.2243804. <https://www.tandfonline.com/doi/full/10.1080/03007995.2023.2243804> (accessed 19/06/2024).
6. Hagen M, Clark K, et al. A real-world study of quality of life following treatment with xylometazoline hydrochloride in individuals with common cold. *Therapeutic Advances in Respiratory Disease* 2024;18. doi:10.1177/17534666241228927. <https://www.ncbi.nlm.gov/pmc/articles/PMC10878222/> (accessed 19/06/2024).

Gender declaration: All references to persons apply equally to all genders. For reasons of better readability, the language forms male, female and diverse (m/f/d) are not used simultaneously.

Conflict of interest: none

Disclosure: Medical writing and publication were funded by the Haleon Group of companies.

Information regarding manuscript

Submitted on: 19.06.2024

Accepted on: 09.07.2024

Published on: 30.07.2024