

# Pain: the use of paracetamol in multimorbid patients

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## ABSTRACT

**Introduction:** More than one third of Italians have at least 2 chronic comorbidities, and this percentage is more than 50% after the age of 75 years. The presence of comorbidities has as a consequence politreatments, with a high probability of drug interactions and adverse events.

**Methods:** Medical literature about physiopathology of pain and its treatments was reviewed and combined with expert opinion of the authors.

**Results:** Pain is “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”. Chronic pain is one of the main factors that impact on quality of life and is the leading reason why patients seek medical care.

Pain can represent a defense against potential or real damage to the body, but chronic pain becomes a disease itself, with a profound negative impact on quality of life. Paracetamol is a drug with analgesic and antipyretic action widely used both alone and in combination with other medications. It is an effective and safe drug, and can be used in infants and elderly, in patients in whom NSAIDs are contraindicated, in pregnant or breastfeeding women. A large number of studies have recognized the efficacy and safety of paracetamol in treating pain, and the drug is included in the WHO's List of Essential Medicines. EULAR, AAOS and NICE guidelines recommend paracetamol as the first-choice analgesic in several conditions like osteoarthritis or post-surgical pain.

**Conclusions:** Paracetamol, due to its efficacy, safety of use, poor interaction with other drugs, appears to be the first-choice treatment of painful syndromes in the elderly patient.

**Keywords:** Pain treatment, paracetamol, elderly

## INTRODUCTION

### Health in Elderly

According to the 2015 ISTAT report, life expectancy in Italy is considerable for citizens aged 65, (18.9 for men and

22.2 for women), one year higher than the average for other European countries; however, elderly people have the lowest health-related quality of life<sup>1</sup>; in the age group between 65 and 69, 37.6% of Italians have at least 2 chronic comorbidities, a percentage that exceeds 50% in the age group of 75-79

years, with severe motor limitations in over 20% of cases<sup>1</sup>.

Chronic pain, mainly caused by musculoskeletal pathologies such as osteoarthritis, lumbar and cervical pathologies, is one of the main factors that impact on quality of life<sup>1</sup>.

The 2019 ISTAT reports a slightly improved situation, with a life expectancy at 65 years of 19.4 years in men and 22.4 years in women, and with an incidence of serious chronic diseases in 46% of men and 41.1% of women over 75 (Fig. 1)<sup>2</sup>.

The presence of multiple comorbidities involves, among others, the problem of multiple treatments, with a high probability of drug interactions and adverse events<sup>3</sup>. A study conducted in Germany on 355 patients aged > 65 years with

chronic pain has been recently published; the study was aimed at evaluating the frequency of multiple comorbidities (presence of  $\geq 2$  concomitant diseases), of polytherapy treatments, defined as the simultaneous prescription of  $\geq 5$  drugs, and the onset of possible drug interactions. The results show that more than half of the patients (55.4%) had comorbidities treated with an average of 9 drugs, and in 89.5% of cases the treatment consisted of  $\geq 5$  drugs (Fig. 2). The authors identified 184 possible interactions in 34% of cases<sup>4</sup>.

A Spanish longitudinal study of 723,016 multimorbid, elderly patients (65–99 years) followed from 2012 to 2016, reported a significant increase over the years of patients with at least one Medication Related Problems (MRPs) (2012:

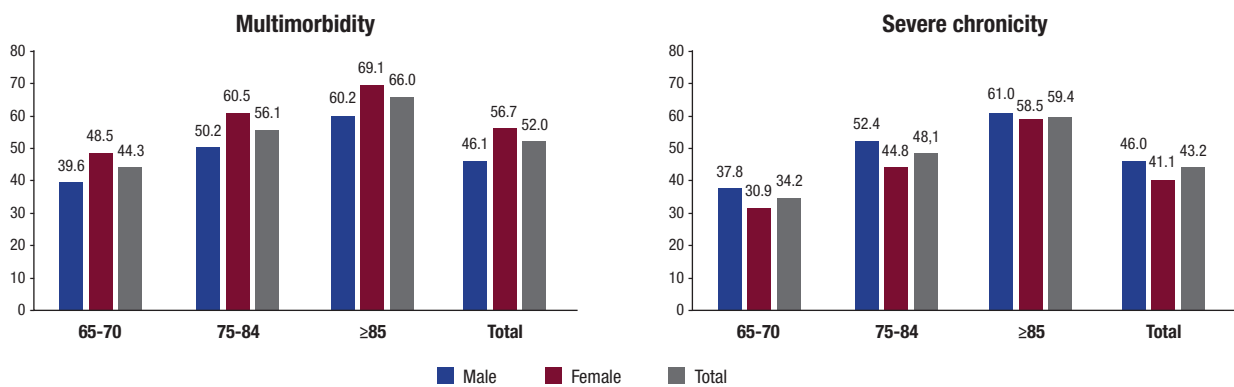


Figure 1. People aged  $\geq 65$  years, by presence of multimorbidity and severe chronicity (year 2019, rate for 100 people) (modified from 2)

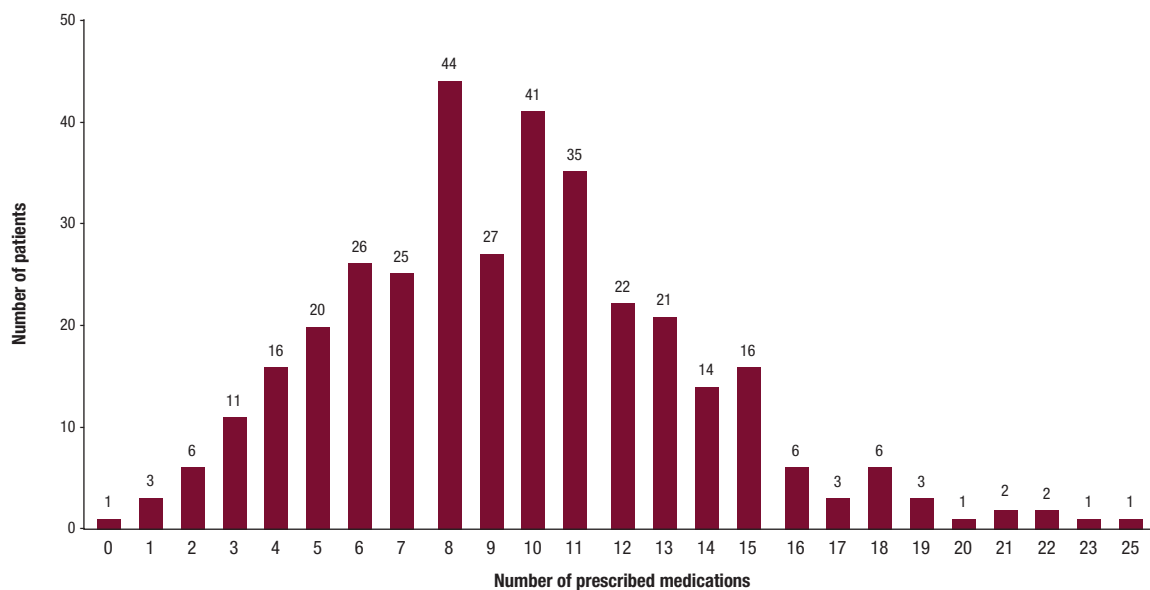


Figure 2. Number of prescribed medications in 355 patient > 65 years (modified from 4)

66.9% ; 2016: 75.5%); MRPs are independently associated with mortality, duplicated therapy and interaction<sup>5</sup>. Zerah et coll. in a study on 1,959 hospitalized elderly patients (mean age 79 years) found that more than half had at least one drug-drug interaction, and this percentage was 57% after 12 months<sup>6</sup>.

In elderly, the incidence of adverse events is higher due to multiple comorbidities and politreatments, and this evidence should be considered with caution when introducing a new drug into the treatment of this type of patients<sup>7</sup>.

## METHODS

### Pain: definition, physiopathology, transmission and psychological aspects

According to International Association of Study of Pain (IASP) definition, pain is “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”<sup>8</sup>.

Pain is a complex sensation linked by the transmission of the painful stimulus from the involved tissues to the brain (nociception); the painful stimulus causes unpleasant sensations that depend not only on its intensity, but also on the modalities in which the patient subjectively perceives and experiences the sensation of pain (pain threshold)<sup>9,10</sup>.

Pain can represent an acute physiological mechanism, a defense against potential or real damage to the body; it is the way by which the Central Nervous System (CNS) is alerted and can avoid or limit the tissue damage<sup>9</sup>.

Acute pain results from activation of specific peripheral pain receptors (nociceptors) and their type A delta and C nerve fibers, which enter the spinal cord at the dorsal root ganglia and release chemical transmitters which activate the second-order pain-transmission neurons located in the gray matter<sup>11</sup>. From here they run in the lateral columns until they reach the thalamus and then the cerebral cortex (spinothalamic pathway)<sup>11,12</sup> (Fig 3).

Acute pain is often associated with anxiety and sympathetic nervous system overactivity (e.g., tachycardia, increased respiratory activity and blood pressure, pupillary dilation). Since the pain changes from acute to chronic it becomes a disease in itself. Chronic pain is related to continuous tissue damage, and is caused by persistent activation of the fibers. It can also result from persistent damage or dysfunction of the peripheral or CNS (neuropathic pain). Chronic pain is generally associated with mood depression and anxiety, and with signs such as fatigue, anorexia, reduced recreational activities and social relationships, with a profound negative impact on quality of life (Fig. 4). Pain, in particular chronic pain, is the leading reason why patients seek medical care, and represents a disabling and burdensome condition<sup>9,13</sup>.

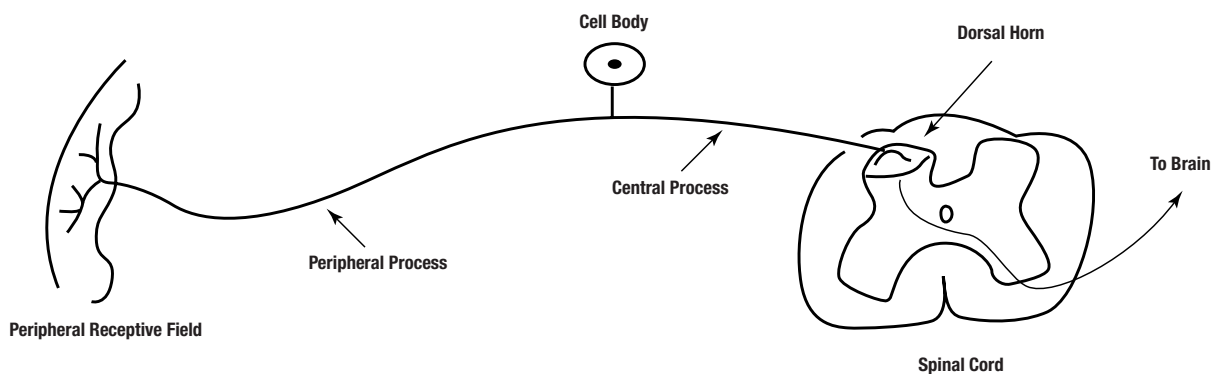
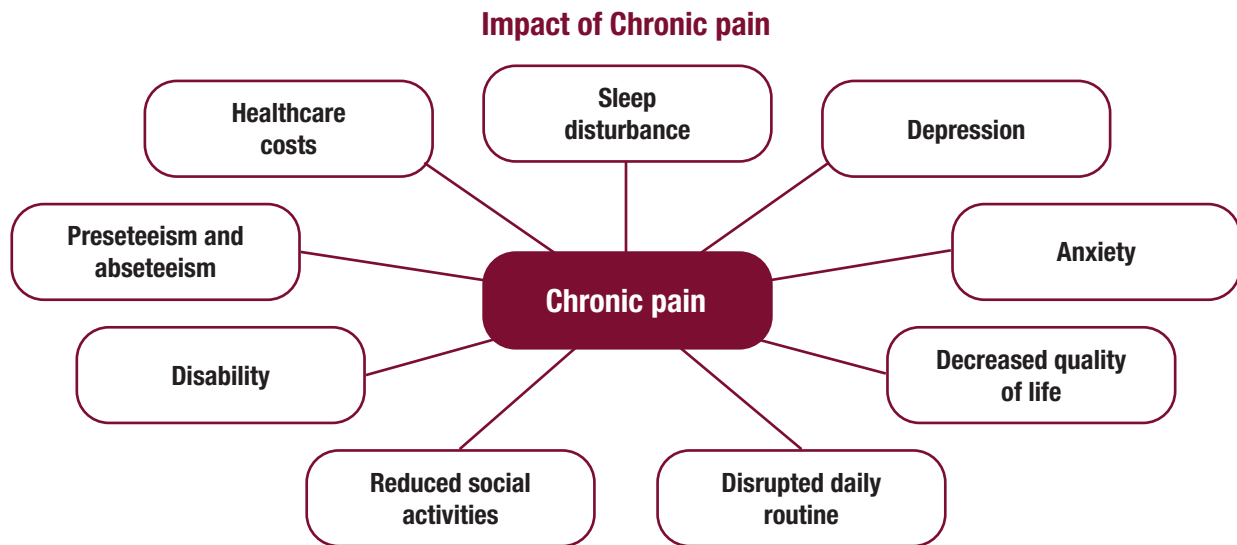


Figure 3. The transmission of painful stimulus from tissue to CNS (modified from 9)



**Figure 4. Impact of chronic Pain on Quality of Life (elaborated from 9, 13)**

### Pharmacological treatment of pain: paracetamol

Many classes of drugs are now available for the treatment of pain, with different route of administration and delivery systems. Among them, the most used are non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antiepileptic drugs, antidepressants, opioids, and local anesthetics<sup>7</sup>.

Paracetamol (or acetaminophen, N-acetyl-para-aminophenol) is a drug with analgesic and antipyretic action widely used both alone and in combination with other medications, for fever due to cold or flu, or for the treatment of acute and chronic pain. It is a safe drug, and can be used, at the proper dosages, in very delicate population groups such as infants and the elderly, such as in patients in whom NSAIDs are contraindicated, i.e. those with gastric ulcers and bronchial asthma, or pregnant and breast-feeding women<sup>14</sup>.

Paracetamol has a lower analgesic action than NSAIDs but is often preferred due to its better tolerability. The mechanism of action of paracetamol is not fully understood, but it is now generally accepted that it inhibits the formation of a phenoxyl radical formation from a critical tyrosine residue, essential for cyclooxygenase activity of COX-2, and consequently the PGs synthesis, powerful sensitizers of nociceptive transmission<sup>15</sup>. Compared with other NSAIDs,

paracetamol has a similar antipyretic and analgesic, but not anti-inflammatory, action, because its activity is inhibited by a high arachidonic acid concentration, present in inflamed tissues<sup>16</sup>.

When arachidonic acid levels are low, paracetamol is able to inhibit COX-2: this condition occurs in the small hypothalamic vessels (paracetamol easily crosses the blood-brain barrier, reaching the CNS)<sup>16</sup> during the febrile response, which paracetamol is therefore able to effectively counteract<sup>17</sup>. The analgesic effects of paracetamol are mainly expressed through some of its metabolites, in particular AM404, which is formed in the spinal cord and in some supraspinal and cerebral areas; AM404 inhibits the reuptake of anandamide, the main endogenous cannabinoid, inducing analgesia (Fig. 5)<sup>14,18,19</sup>.

Paracetamol is water-soluble and after oral administration is rapidly absorbed in the first part of the small intestine with a high bioavailability (70 to 90%). It is also well absorbed by the rectal mucosa. Its maximum plasmatic concentration is reached in about 30-60 minutes; Its distribution is fast and uniform in most tissues and fluids with a distribution volume of approximately 0.9 l / kg. The drug is mainly metabolized by the liver and 85-95% excreted in the urine within 24 hours, mainly as sulphate and glucuronate; in the

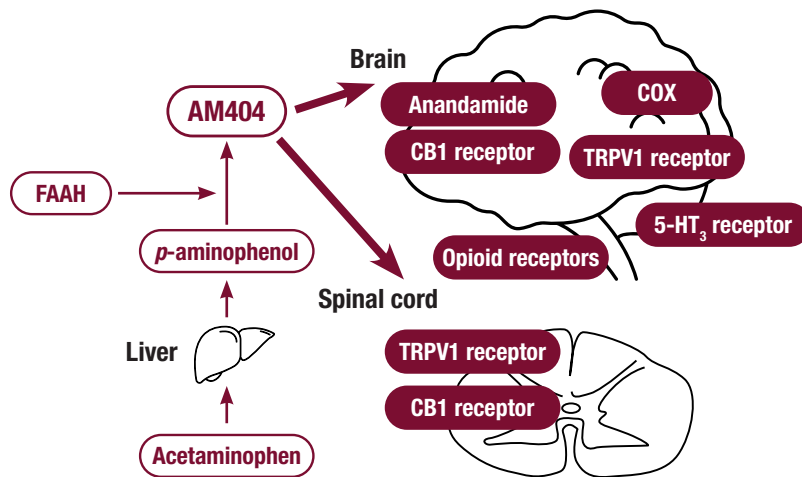


Figure 5. Paracetamol mechanism of action (modified from 14)

course of hepatic metabolism a small amount of the drug is converted into a highly reactive alkylating metabolite, inactivated by reduced glutathione (Fig. 6). Overdose of paracetamol causes glutathione depletion, with possible acute liver necrosis, which can be prevented by early administration of methionine and N-acetylcysteine. The plasma half-life ranges from 1.9 to 2.5 hours and the total body clearance from 4.5 to 5.5 ml / kg / min<sup>20</sup>.

At recommended doses, few clinically significant drugs interactions have been documented between paracetamol and

other medications. There is considerable controversy over the possible increase in the anticoagulant effect of warfarin, but no serious adverse events have been confirmed in humans at therapeutic doses. Since the absorption of paracetamol is dependent on the gastric content, drugs that alter gastric emptying can modify its pharmacokinetics; but this would not cause serious negative effects<sup>21,22</sup>. Paracetamol has no effect with the antithrombotic action of salicylic acid<sup>23</sup>. At normal dosages no evidence of a higher incidence of hepatotoxicity has been found in older subjects, and for

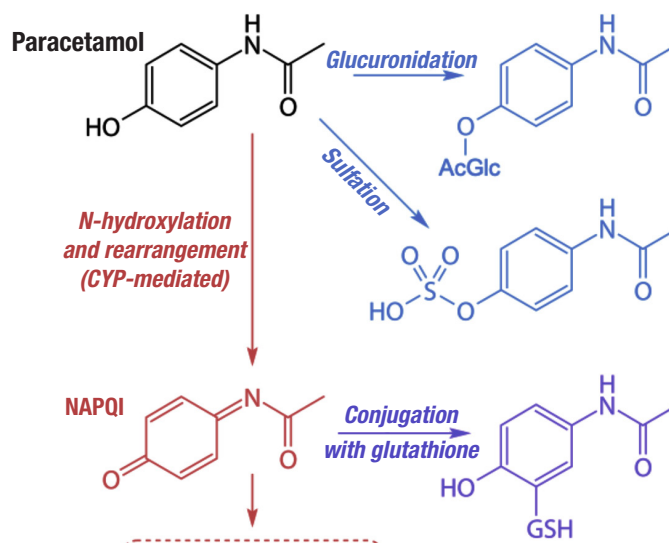


Figure 6. Paracetamol and its metabolism (elaborated from 20)

this reason it is the most commonly used analgesic in the aged patients<sup>24,25</sup>.

## DISCUSSION

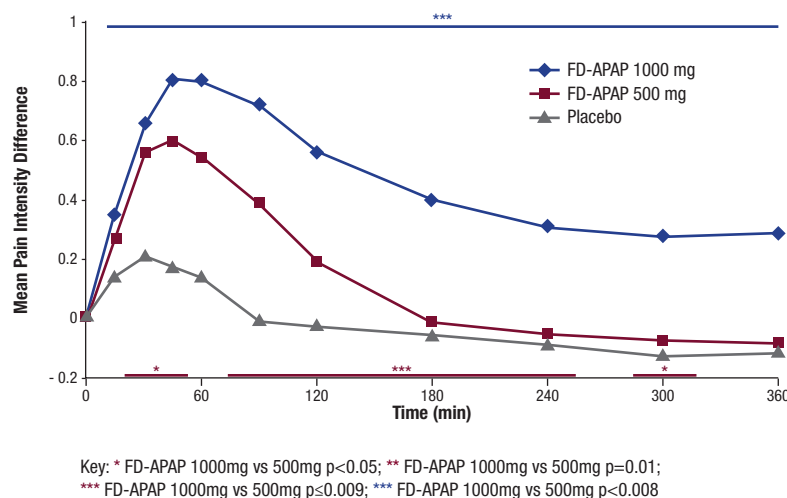
Paracetamol has an effective analgesic action with a high therapeutic index in postoperative and inflammatory pain, with no known abuse potential<sup>17,26-28</sup>. It is the most widely used pain reliever in the United States, where it is taken by about 50 million Americans every week<sup>29</sup>. A large number of studies have recognized the efficacy and safety of paracetamol in treating pain, and the drug is included in the WHO's List of Essential Medicines. In particular, it is present in the list of treatments for pain and palliative care, and among drugs for the treatment of acute attack of migraine<sup>30</sup>. For the management of patients with mild to moderate osteoarticular pain, paracetamol should be considered the analgesic of first choice<sup>17,31-33</sup>. For its efficacy and safety, the use of paracetamol is recommended by the European Alliance of Associations for Rheumatology (EULAR) guidelines at doses up to 4 g / day as the first-choice oral analgesic in several conditions, like osteoarthritis of hip and knee<sup>31,32</sup> and psoriatic arthritis<sup>33</sup>. The American Academy of Orthopedic Surgery (AAOS) guidelines recommend paracetamol for post-surgical pain management<sup>34</sup>; the National Institute for Health and Care Excellence (NICE) guidelines also include paracetamol for

various indications, such as osteoarthritis<sup>35</sup>, hip fractures<sup>36</sup>, non-complex fractures<sup>37</sup>, perioperative pain<sup>38</sup> and others. Moreover, paracetamol has been shown to be highly effective, safe and well tolerated in the treatment of pain, functional disability, photophobia and phonophobia in the treatment of acute migraine attack<sup>27,39,40</sup>. The analgesic efficacy of paracetamol in the treatment of mild to moderate acute pain is dose dependent, and the dosage of 1000 mg shows a higher effect than lower dosages, as reported by Gault in a review of comparative trials<sup>41</sup> (Fig. 7).

Paracetamol has different and complementary mechanisms of action compared to other analgesic drugs: this justify its use in combination therapies with opiates (codeine, tramadol and oxycodone) and NSAIDs (ibuprofen)<sup>16</sup>.

## CONCLUSIONS

The care of elderly patients with co-morbidities and in polytherapy is a problem that health systems will have to deal with more and more frequently. In daily clinical practice, a "disease oriented" approach is still too often adopted for all patients, but it is appropriate when the patients have a single predominant disease, as occurs in clinical trials, to obtain a specific outcome like a survival increase or a stroke prevention. This approach is unsuitable, however, in elderly



**Figure 7. Mean pain intensity difference from 15 minutes to six hours for patients undergoing surgical removal of impacted molar (modified from 41)**

people, who are almost always affected by multiple, chronic pathologies and treated with multiple therapies, because inevitably brings to a fragmentation of care. A patient oriented system implies that the patient as a whole is the main driver of therapeutic choices, and that the outcomes include not only efficacy, but also the maintenance of safety, with an improvement in the quality of life. This approach minimizes the risk of pharmacological interferences and ADRs (adverse reactions), largely documented scientific literature.

The progressive aging of the population is frequently characterized by the presence of painful pathologies mostly caused by osteoarticular problems, with limitations in fun-

ctional autonomy, and disability that significantly affects the quality of life. The choice of drugs to be used in pain therapy for the treatment of multimorbid elderly cannot ignore this and must be periodically re-evaluated in order to verify that the therapeutic objectives are achieved while maintaining safety. Paracetamol, acting on pain with multiple mechanisms, may be used either alone, or in synergy with other medications (NSAIDs, opioids) and thanks to its efficacy, safety of use and poor drug interaction, it can represent the first choice for painful syndromes in the elderly patient, as underlined by various guidelines that drive the treatment of this type of pathology.

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## DISCLOSURES

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